DONALD SPECTER – 083925
STEVEN FAMA – 099641
MARGOT MENDELSON – 268583
PRISON LAW OFFICE
1917 Fifth Street
Berkeley, California 94710-1916
Telephone: (510) 280-2621

CLAUDIA CENTER – 158255
DISABILITY RIGHTS EDUCATION
AND DEFENSE FUND, INC.
Ed Roberts Campus
3075 Adeline Street, Suite 210
Berkeley, California 94703-2578
Telephone: (510) 644-2555

MICHAEL W. BIEN – 096891
JEFFREY L. BORNSTEIN – 099358
ERNEST GALVAN – 196065
THOMAS NOLAN – 169692
LISA ELLS – 243657
JENNY S. YELIN – 273601
MICHAEL S. NUNEZ – 280535
JESSICA WINTER – 294237
MARC J. SHINN-KRANTZ – 312968
CARA E. TRAPANI – 313411
ALEXANDER GOURSE – 321631
AMY XU – 330707
ROSEN BIEN
GALVAN & GRUNFELD LLP
101 Mission Street, Sixth Floor
San Francisco, California 94105-1738
Telephone: (415) 433-6830

Attorneys for Plaintiffs

UNITED STATES DISTRICT COURT

EASTERN DISTRICT OF CALIFORNIA

RALPH COLEMAN, et al.,

Plaintiffs,

v.

GAVIN NEWSOM, et al.,

Defendants.

Case No. 2:90-CV-00520-KJM-DB

DECLARATION OF MICHAEL W. BIEN IN SUPPORT OF PLAINTIFFS' BRIEF RE: EVIDENCE SUPPORTING SERIOUS MENTAL ILLNESS AS RISK FACTOR FOR COVID-19 AND NEED FOR ADDITIONAL MENTAL HEALTH INTERVENTIONS

Judge: Hon. Kimberly J. Mueller
Crtrm.: 3, 15th Floor, Sacramento

I, Michael W. Bien, declare:

1. I am an attorney duly admitted to practice before this Court. I am a partner in the law firm of Rosen Bien Galvan & Grunfeld LLP, counsel of record for Plaintiffs. I have personal knowledge of the facts set forth herein, and if called as a witness, I could competently so testify. I make this declaration in support of Plaintiffs' Brief Re Evidence Supporting Serious Mental Illness as Risk Factor for COVID-19 and Need for Additional Mental Health Interventions.

2. My office accessed the California Correctional Health Care Services (CCHCS) COVID-19 Monitoring Patient Registry on Wednesday, July 1 at approximately 8:36 a.m. The Registry is a log of CDCR incarcerated patients who have tested positive for COVID-19. The Registry includes patients whose COVID-19 cases are deemed resolved, but it excludes patients who are deceased or who have been released from custody. My office also accessed a version of the Registry filtered to show all patients who are "Out to Hospital." A redacted excerpt of a sample of the unfiltered version of the Registry is attached hereto as **Exhibit 1**. Given that the Registry is now hundreds of pages long and also contains patient information that would require redaction, I have attached only a redacted excerpt here. I am prepared to file or lodge *in camera* a full copy of the filtered and unfiltered versions of the Registry at the Court's request. The Registry can be downloaded in multiple formats including PDF and Excel.

3. The Registry showed 4,808 incarcerated patients including 1,275 *Coleman* class members. The filtered Registry showed 62 patients who were hospitalized. I calculated the average mean age of the hospitalized patients was 61.3 and the median age was 61.5. The range was from 84 to 32. Of the hospitalized patients, 40% were *Coleman* class members (25/62), six EOP and 19 CCCMS; 44% were *Armstrong* class members (27/62), and 21% were listed in the "DDP" disability column (13/62) (including members of the *Clark* class in the Developmental Disability Program, *Armstrong* Learning Disability, TABE score or reading level under grade 4). Many of the patients are members of more than one group (medical high risk, *Coleman*, *Armstrong*, *Clark*). Only 3% of the

hospitalized patients (2/62) were not identified as 55 or older, a *Coleman*, *Armstrong* or *Clark* class member or high risk medical.

4. We are provided with the identity of each CDCR incarcerated person who dies as a result of COVID-19. My office tracks and analyzes that data using information from medical and CDCR records. As of 3:00 p.m. on June 29, CDCR informed us of 22 deaths from COVID-19: 16 were from CIM, three from Avenal, two from CVSP and one from CIW. The average mean age of the patients who died was 62.6 and the median was 63. The range was from 83 to 41. Of the patients who died, 41% were *Coleman* class members participating in the Mental Health Services Delivery System (MHSDS) at the time of their deaths (9/22), and two additional patients had recent MHSDS histories evident in their medical records, 50% were *Armstrong* class members (11/22) and 18% were in the Developmental Disability Program (4/22) (*Clark* class or *Armstrong* Learning Disability, TABE score, reading level, under grade 4). Many of the patients who died were members of more than one group (medical high risk, *Coleman*, *Armstrong*, *Clark*). All of the patients who died (22/22) were either 55 or older, a *Coleman*, *Armstrong*, or *Clark* class member, or high risk medical. For 20 of the 22 deaths, we have information about race and ethnicity: 75% were people of color (9-Hispanic, 3-Black, 2-Asian/Pacific Islander and 1-American Indian/Alaskan Native). I am informed that one additional recently deceased class member, whose cause of death CDCR has not yet confirmed, tested positive for COVID-19 after his death. This person was 71 years old, a *Coleman* and *Armstrong* class member participant in the MHSDS at the CCCMS level of care, and incarcerated at San Quentin State Prison's Death Row.

5. Attached hereto as **Exhibit 2** is a true and correct copy of a study by the Centers for Disease Control and Prevention ("CDC"), dated June 15, 2020, entitled "Morbidity and Mortality Weekly Report: Coronavirus Disease 2019 Case Surveillance – United States, January 22-May 30, 2020, Vol. 69," available at https://www.cdc.gov/mmwr/volumes/69/wr/pdfs/mm6924e2-H.pdf. This recently published CDC study analyzes all reported cases of COVID-19 in the United States from

January 22 through May 30, 2020—1,320,488 lab confirmed cases—and measures demographic characteristics, underlying medical conditions and outcomes.

6. The CDC study found solid confirmation that underlying conditions, including psychological/psychiatric conditions, are the most important predictor of adverse outcomes from infection with COVID-19. Hospitalizations were six times higher among patients with a reported underlying condition (45.4%) than those without (7.6%). Deaths were 12 times higher among patients with reported underlying conditions (19.5%) compared to those without underlying conditions (1.6%). The percentage of ICU admissions among persons with underlying conditions age 60-69 was 11%, and for those age 70-79 was 12%. The death rate for persons age 80 and over with at least one underlying condition was 50% (compared to 30% for those 80 and older without an underlying condition).

7. For purposes of the study, CDC defined "underlying health conditions" as diabetes, cardiovascular disease, severe obesity, chronic renal, liver or lung disease, immuno-compromised condition, autoimmune condition and neurologic condition including neurodevelopmental, intellectual, physical, visual, or hearing impairment, or psychological/psychiatric condition, or other medical condition. *See* **Exhibit 2** at 762, tbl 2 & n.*. That is, people with psychiatric, developmental, and physical disabilities as well as people who are deaf, hard of hearing, or blind, are also at high risk for adverse outcomes from COVID-19.

8. Advanced age is even more of a risk factor than previously known: According to the CDC study, older adults are far more likely to contract COVID-19 than average and are also far more likely to be hospitalized and die. While the overall incidence of infection was 403 cases per 100,000 (median age 48), the per-100,000 incidence for children under nine was 51, the incidence for people ages 70-79 was 464, and the incidence for people age 80 and older was 902. Overall, 14% of patients were hospitalized, 2% admitted to ICU and 5% died, while 28% of the patients who were 80 and over died.

9. Distinctions by race and ethnicity continue to be extremely significant: According to the CDC study, of all COVID-19 cases with known race and ethnicity 33% were Hispanic, 22% were Black, and 1.3% were Native American while these groups respectively account for 18%, 13%, and 0.7% of the overall population in the United States. The racial disparities in all aspects of our society are sharply visible in the pandemic.

10. On June 19, 2020, in response to the Court's questions and Dr. Joseph Bick's assertions at the June 12, 2020 status conference, Plaintiffs sent a letter to Defendants and the Special Master gathering resources including scientific research and public health guidance demonstrating a strong link between serious mental illness and COVID-19. The letter also explained, in light of the novelty of the pandemic, the need for CDCR's COVID-19 response to rely in part on research and guidance regarding analogous medical or behavioral conditions, and common sense. On June 23, 2020, during the Twenty-Third COVID-19 Taskforce meeting led by the Special Master, the parties briefly discussed the issues raised in Plaintiffs' letter. At the June 26, 2020 status conference in this matter, Plaintiffs informed the Court of these materials and Defendants confirmed that addressing the materials required additional discussions and work.

11. Attached hereto as **Exhibit 3** is a true and correct copy of guidance from the Department of Health & Human Services, Centers for Medicare and Medicaid Services, dated March 30, 2020, entitled "Guidance for Infection Control and Prevention of Coronavirus Disease (COVID-19) in Hospitals, Psychiatric Hospitals, and Critical Access Hospitals (CAHs): FAQs, Considerations for Patient Triage, Placement, Limits to Visitation and Availability of 1135 waivers," available at https://www.cms.gov/files/document/qso-20-13-hospitals-cahs-revised.pdf.

12. Attached hereto as **Exhibit 4** is a true and correct copy of guidance from the Department of Health & Human Services, Centers for Medicare and Medicaid Services, dated March 30, 2020, entitled "Guidance for Infection Control and Prevention of Coronavirus Disease 2019 (COVID-19) in Intermediate Care Facilities for Individuals with

Intellectual Disabilities (ICF/IIDs) and Psychiatric Residential Treatment Facilities (PRTFs)," available at https://www.cms.gov/files/document/qso-20-23-icf-iid-prtf.pdf.

13. Attached hereto as **Exhibit 5** is a true and correct copy of guidance from the CDC, dated April 7, 2020, entitled "Coronavirus Disease 2019 (COVID-19): People with Disabilities," available at https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-with-disabilities.html.

14. Attached hereto as **Exhibit 6** is a true and correct copy of an article by Julia Reis, published by *Healthline*, dated April 7, 2020, entitled "COVID-19 Can Have Serious Effects on People with Mental Health Disorders," available at https://www.healthline.com/health-news/covid-19-serious-effects-people-with-mental-health-disorders.

15. Attached hereto as **Exhibit 7** is a true and correct copy of an article by Benjamin G. Druss, published by *JAMA Psychiatry*, dated April 3, 2020, entitled "Addressing the COVID-19 Pandemic in Populations With Serious Mental Illness," available at https://jamanetwork.com/journals/jamapsychiatry/fullarticle/2764227.

16. Attached hereto as **Exhibit 8** is a true and correct copy of an article by Nicole M. Benson, et al., published by *The Lancet*, dated May 11, 2020, entitled "COVID-19 Testing and Patients in Mental Health Facilities," available at https://www.thelancet.com/action/showPdf?pii=S2215-0366%2820%2930198-X.

17. Attached hereto as **Exhibit 9** is a true and correct copy of an article by Andrea Fiorillo, et al., published by *Psychiatric Times*, dated May 15, 2020, entitled "Psychosocial Interventions to Reduce Premature Mortality in Patients With Serious Mental Illness," available at https://www.psychiatrictimes.com/special-reports/psychosocial-interventions-reduce-premature-mortality-patients-serious-mental-illness.

18. Attached hereto as **Exhibit 10** is a true and correct copy of an article by Joseph Shapiro, published by NPR, dated June 9, 2020, entitled "COVID-19 Infections And Deaths Are Higher Among Those With Intellectual Disabilities," available at

https://www.npr.org/2020/06/09/872401607/covid-19-infections-and-deaths-are-higher-among-those-with-intellectual-disabili.

19. Attached hereto as **Exhibit 11** is a true and correct copy of an article by Marla Milling, published by *Forbes*, dated May 28, 2020, entitled "People with Intellectual and Developmental Disabilities More Likely to Die from COVID-19," available at https://www.forbes.com/sites/marlamilling/2020/05/28/people-with-intellectual-and-developmental-disabilities-more-likely-to-die-from-covid-19/#87a10bb33159.

20. Attached hereto as **Exhibit 12** is a true and correct copy of an information sheet from the Alzheimer's Association, accessed on June 29, 2020, entitled "Coronavirus (COVID-19): Tips for Dementia Caregivers," available at https://www.dhcs.ca.gov/Documents/COVID-19/Alzheimers-Association-Guidance-on-COVID-19.pdf.

21. Attached hereto as **Exhibit 13** is a true and correct copy of guidance from the World Health Organization ("WHO"), dated 2018, entitled "Management of Physical Health Conditions in Adults with Severe Mental Disorders," available at https://apps.who.int/iris/bitstream/handle/10665/275718/9789241550383-eng.pdf.

22. Attached hereto as **Exhibit 14** is a true and correct copy of an article by Matthew J. Akiyama, et al., published by *New England Journal of Medicine,* dated May 28, 2020, entitled "Flattening the Curve for Incarcerated Populations – COVID 19 in Jails and Prisons," available at https://www.nejm.org/doi/10.1056/NEJMp2005687.

23. Attached hereto as **Exhibit 15** is a true and correct excerpted copy of a letter from over 3,000 medical professionals to the U.S. Immigration and Customs Enforcement (ICE) agency, dated March 13, 2020, entitled "Open Letter to ICE from Medical Professionals Regarding COVID-19," available at https://nylpi.org/wp-content/uploads/2020/03/FINAL-LETTER-Open-Letter-to-ICE-From-Medical-Professionals-Regarding-COVID-19.pdf. Due to the lengthy list of over 3,000 medical professional signatories—spanning 66 pages—I have excerpted the letter to include only the first page of signatories. The full list is available at the above link.

24. Attached hereto as **Exhibit 16** is a true and correct copy of an article by Laura M. Maruschak, et al., published by the *American Journal of Public Health*, dated October 2009, entitled "Pandemic Influenza and Jail Facilities and Populations," available at https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4504367/.

25. Attached hereto as **Exhibit 17** is a true and correct copy of an article by Catherine Kariuki-Nyuthea, et al., published in *Comorbidity of Mental and Physical Disorders*, dated 2015 (print version), entitled "Anxiety and Related Disorders and Physical Illness" available at https://www.karger.com/Article/Pdf/365538.

26. Attached hereto as **Exhibit 18** is a true and correct copy of an article by Joshua D. Rosenblat, et al., published in *Brain Sciences*, dated October 30, 2017, entitled "Bipolar Disorder and Immune Dysfunction: Epidemiological Findings, Proposed Pathophysiology and Clinical Implications," available at https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5704151/pdf/brainsci-07-00144.pdf.

27. Attached hereto as **Exhibit 19** is a true and correct copy of an article by Janice K. Kiecolt-Glasera, et al., published in the *Journal of Psychosomatic Research*, dated 2002, entitled "Depression and immune function: Central pathways to morbidity and mortality," available at http://pni.osumc.edu/KG%20Publications%20(pdf)/154.pdf.

28. Attached hereto as **Exhibit 20** is a true and correct copy of an article by the American Psychological Association, dated February 23, 2006, entitled "Stress Weakens the Immune System," available at https://www.apa.org/research/action/immune.

29. Attached hereto as **Exhibit 21** is a true and correct copy of the Author Manuscript version of an article by Gretchen N. Neigh, et al., published in the *Current Opinion in Pharmacology*, dated August 2016, entitled "Co-Morbidity of PTSD and Immune System Dysfunction: Opportunities for Treatment," available at https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4992603/pdf/nihms805030.pdf.

30. Attached hereto as **Exhibit 22** is a true and correct copy of an article by Sukanta Saha, et al., published in *Archives of General Psychiatry*, dated 2007, entitled "A Systematic Review of Mortality in Schizophrenia, Is the Differential Mortality Gap

Worsening Over Time," available at https://jamanetwork.com/journals/jamapsychiatry/fullarticle/210034.

31. Attached hereto as **Exhibit 23** is a true and correct copy of an article by Keramet Reiter, et al., published in the *American Journal of Public Health*, dated January 1, 2020, entitled "Psychological Distress in Solitary Confinement: Symptoms, Severity, and Prevalence in the United States, 2017–2018," available at https://ajph.aphapublications.org/doi/10.2105/AJPH.2019.305375.

32. Attached hereto as **Exhibit 24** is a true and correct copy of an article by Jeffrey L. Metzner, et al., published in the *Journal of the American Academy of Psychiatry and the Law*, dated 2010, entitled "Solitary Confinement and Mental Illness in U.S. Prisons: A Challenge for Medical Ethics," available at http://jaapl.org/content/jaapl/38/1/104.full.pdf.

33. Attached hereto as **Exhibit 25** is a true and correct copy of the Brief of Amici Curiae Professors and Practitioners of Psychiatry and Psychology in Support of Petitioner, *Prieto v. Clarke*, No. 15-31, 2015 WL 4720278 (U.S. Aug. 5, 2015), available at https://www.scotusblog.com/wp-content/uploads/2015/10/PrietoClarke_AmicusMentalHealthExperts.pdf.

34. Attached hereto as **Exhibit 26** is a true and correct copy of an article by Craig Haney, published in *Crime and Justice*, dated March 9, 2018, entitled "The Psychological Effects of Solitary Confinement: A Systematic Critique" available at https://www.researchgate.net/publication/323674531_The_Psychological_Effects_of_Solitary_Confinement_A_Systematic_Critique.

35. Attached hereto as **Exhibit 27** is a true and correct copy of an article by Stuart Grassian, published in the *Washington University Journal of Law & Policy*, dated 2006, entitled "Psychiatric Effects of Solitary Confinement," available at https://openscholarship.wustl.edu/cgi/viewcontent.cgi?article=1362&context=law_journal_law_policy.

36. Attached hereto as **Exhibit 28** is a true and correct copy of an excerpt of relevant pages from the California Code of Regulations Title 15 Inmate Property; Matrix – Authorized Personal Property Schedule, last revised April 1, 2014, available at https://www.cdcr.ca.gov/regulations/wp-content/uploads/sites/171/2019/08/APPS-Rev-4-1-14.pdf?label=Authorized%20Personal%20Property%20Schedule%20(APPS)%20(Rev.%204/1/14)&from=https://www.cdcr.ca.gov/regulations/cdcr-regulations/dom-appendices/.

37. Attached hereto as **Exhibit 29** is a true and correct copy of the Declaration of Robert M. Sapolsky filed in *Arevalo v. Decker*, No. 1:20-cv-02982, Dkt. 3-3 (S.D.N.Y. Apr. 13, 2020), available at https://federaldefendersny.org/pdfs/2020.05.11%20CLE/Abrego%20v.%20Decker%20-%20Sapolsky%20Decl.%20and%20CV%20(1)_Redacted%5B1%5D.pdf (redactions in original).

38. Attached hereto as **Exhibit 30** is a true and correct copy of an article by Jeffrey L. Geller, et al., published by the American Psychiatric Association, *Psychiatric News*, dated April 7, 2020, entitled "Patients With SMI in the Age of COVID-19: What Psychiatrists Need to Know" available at https://doi.org/10.1176/appi.pn.2020.4b39.

39. Attached hereto as **Exhibit 31** is a true and correct copy of an article by Ann K. Shinn, et al., published by the *Journal of Clinical Psychiatry*, dated 2020, last accessed June 30, 2020, entitled "Perspectives on the COVID-19 Pandemic and Individuals With Serious Mental Illness," available at https://www.psychiatrist.com/JCP/article/Pages/2020/v81/20com13412.aspx.

40. Attached hereto as **Exhibit 32** is a true and correct copy of a memorandum by AMEND: Changing Correctional Culture, dated June 15, 2020, entitled "Urgent Memo: COVID-19 Outbreak: San Quentin State Prison," available at https://amend.us/wp-content/uploads/2020/06/COVID19-Outbreak-SQ-Prison-6.15.2020.pdf.

41. Attached hereto as **Exhibit 33** is a true and correct copy of a memorandum by David Cloud, et al., published by AMEND: Changing Correctional Culture, dated April

9, 2020, entitled "The Ethical Use of Medical Isolation – Not Solitary Confinement – to Reduce COVID-19 Transmission in Correctional Settings," available at https://amend.us/wp-content/uploads/2020/04/Medical-Isolation-vs-Solitary_Amend.pdf.

42. Attached hereto as **Exhibit 34** is a true and correct copy of an article by Aravinthan Varatharaj, et al., entitled Neurological and Neuropsychiatric Complications of COVID-19 in 153 Patients: A UK-Wide Surveillance Study, published in *The Lancet*, dated June 25, 2020, available at https://www.thelancet.com/journals/lanpsy/article/PIIS2215-0366(20)30287-X/fulltext.

43. Attached hereto as **Exhibit 35** is a true and correct copy of guidance from the CDC dated June 25, 2020, entitled "Preparing for COVID-19 in Nursing Homes," available at https://www.cdc.gov/coronavirus/2019-ncov/hcp/long-term-care.html.

44. Attached hereto as **Exhibit 36** is a true and correct copy of guidance from the CDC dated May 27, 2020, entitled "People with Developmental and Behavioral Disabilities," available at https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-with-developmental-behavioral-disabilities.html.

I declare under penalty of perjury under the laws of the United States of America that the foregoing is true and correct, and that this declaration is executed at San Francisco, California this 2d day of July, 2020.

/s/ Michael W. Bien
Michael W. Bien

EXHIBIT 1

COVID MONITORING

Registry Definition

Statewide or Multiple Institutions

Identification & Housing									COVID Status			
Current Institution	First Testing Institution	CDCR#	Last Name	Age	Care Team	Housing Facility	Cell Bed	MHLOC	COVID Status	COVID Risk Factor Count	COVID Weighted Risk Score	First Positive Test
CRC	CRC	[redacted]	[redacted]	38	Facility D1	CRC-D	[redacted]	CCCMS	Confirmed Active	0	0	6/29/2020
CRC	CRC	[redacted]	[redacted]	46	Facility D1	CRC-D	[redacted]		Confirmed Active	0	0	6/29/2020
CRC	CRC	[redacted]	[redacted]	52	Facility D2	CRC-D	[redacted]		Confirmed Active	0	0	6/29/2020
SQ	SQ	[redacted]	[redacted]	44	WB 1	SQ-A	[redacted]		Confirmed Active	0	0	6/29/2020
SQ	SQ	[redacted]	[redacted]	43	WB 2	SQ-A	[redacted]		Confirmed Active	0	0	6/29/2020
SQ	SQ	[redacted]	[redacted]	59	NSEG	SQ-A	[redacted]		Confirmed Active	1	1	6/29/2020
SQ	SQ	[redacted]	[redacted]	54	NSEG	SQ-A	[redacted]		Confirmed Active	0	0	6/29/2020
SQ	SQ	[redacted]	[redacted]	58	WB 1	SQ-A	[redacted]		Confirmed Active	0	0	6/29/2020
SQ	SQ	[redacted]	[redacted]	48	WB 1	SQ-A	[redacted]	CCCMS	Confirmed Active	0	0	6/29/2020
SQ	SQ	[redacted]	[redacted]	56	WB 2	SQ-A	[redacted]		Confirmed Active	1	1	6/29/2020
SQ	SQ	[redacted]	[redacted]	61	WB 1	SQ-A	[redacted]		Confirmed Active	1	1	6/29/2020
SQ	SQ	[redacted]	[redacted]	70	NSEG	SQ-A	[redacted]		Confirmed Active	1	4	6/29/2020

Institution(s): Multiple
Care Team(s): All
Housing/Facility: All

Report run: 7/1/2020 8:36:06 AM

COVID MONITORING

Registry Definition

Statewide or Multiple Institutions

Disability	
DDP	DPP
TABE < 4.0	
TABE < 4.0	

Institution(s): Multiple
Care Team(s): All
Housing/Facility: All

Report run: 7/1/2020 8:36:06 AM

EXHIBIT 2

Morbidity and Mortality Weekly Report

Coronavirus Disease 2019 Case Surveillance — United States, January 22–May 30, 2020

Erin K. Stokes, MPH[1,*]; Laura D. Zambrano, PhD[1,*]; Kayla N. Anderson, PhD[1]; Ellyn P. Marder, DrPH[1]; Kala M. Raz, MPH[1]; Suad El Burai Felix, MPH[1]; Yunfeng Tie, PhD[1]; Kathleen E. Fullerton, MPH[1]

On June 15, 2020, this report was posted as an MMWR *Early Release on the* MMWR *website (https://www.cdc.gov/mmwr).*

The coronavirus disease 2019 (COVID-19) pandemic resulted in 5,817,385 reported cases and 362,705 deaths worldwide through May, 30, 2020,† including 1,761,503 aggregated reported cases and 103,700 deaths in the United States.§ Previous analyses during February–early April 2020 indicated that age ≥65 years and underlying health conditions were associated with a higher risk for severe outcomes, which were less common among children aged <18 years (*1–3*). This report describes demographic characteristics, underlying health conditions, symptoms, and outcomes among 1,320,488 laboratory-confirmed COVID-19 cases individually reported to CDC during January 22–May 30, 2020. Cumulative incidence, 403.6 cases per 100,000 persons,¶ was similar among males (401.1) and females (406.0) and highest among persons aged ≥80 years (902.0). Among 599,636 (45%) cases with known information, 33% of persons were Hispanic or Latino of any race (Hispanic), 22% were non-Hispanic black (black), and 1.3% were non-Hispanic American Indian or Alaska Native (AI/AN). Among 287,320 (22%) cases with sufficient data on underlying health conditions, the most common were cardiovascular disease (32%), diabetes (30%), and chronic lung disease (18%). Overall, 184,673 (14%) patients were hospitalized, 29,837 (2%) were admitted to an intensive care unit (ICU), and 71,116 (5%) died. Hospitalizations were six times higher among patients with a reported underlying condition (45.4%) than those without reported underlying conditions (7.6%). Deaths were 12 times higher among patients with reported underlying conditions (19.5%) compared with those without reported underlying conditions (1.6%). The COVID-19 pandemic continues to be severe, particularly in certain population groups. These preliminary findings underscore the need to build on current efforts to collect and analyze case data, especially among those with underlying health conditions. These data are used to monitor trends in COVID-19 illness, identify and respond to localized incidence increase, and inform policies and practices designed to reduce transmission in the United States.

State and territorial health departments report daily aggregate counts of COVID-19 cases and deaths to CDC; these were tabulated according to date of report to examine reporting trends during January 22–May 30. In addition to aggregate counts, individual COVID-19 case reports were submitted via a CDC COVID-19 case report form** and the National Notifiable Diseases Surveillance System (NNDSS).†† Jurisdictions voluntarily report confirmed and probable§§ cases from reports submitted by health care providers and laboratories. A laboratory-confirmed COVID-19 case was defined as a person with a positive test result for SARS-CoV-2, the virus that causes COVID-19, from a respiratory specimen, using real-time reverse transcription–polymerase chain reaction testing. COVID-19 case data reported from 50 states, New York City, and the District of Columbia¶¶ were analyzed to examine reported demographic characteristics, underlying health conditions, clinical signs and symptoms, and severe outcomes, including hospitalization, ICU admission, and death. Data were missing for age, sex, and race or ethnicity in

*These authors contributed equally to this report.

† https://www.who.int/emergencies/diseases/novel-coronavirus-2019/situation-reports.

§ CDC official counts of cases and deaths, released daily on https://www.cdc.gov/coronavirus/2019-ncov/cases-updates/cases-in-us.html, are aggregate counts from reporting jurisdictions. Throughout the COVID-19 pandemic, CDC has been tracking both aggregate and individual (i.e., line-list) counts of cases and deaths. For aggregate counts, from January 22 to March 2, 2020, CDC provided laboratory confirmation for all U.S. confirmed cases. Starting March 3, jurisdiction partners validated aggregate counts each night for report out at 12 p.m. the following day by CDC. For individual counts, jurisdiction partners electronically submit standardized information for individual cases of COVID-19 to CDC. From April 14, aggregate and individual counts included confirmed and probable cases and deaths, according to the Council of State and Territorial Epidemiologists position statement Interim 20-ID-01 (https://cdn.ymaws.com/www.cste.org/resource/resmgr/2020ps/interim-20-id-01_covid-19.pdf; https://wwwn.cdc.gov/nndss/conditions/coronavirus-disease-2019-covid-19/case-definition/2020/).

¶ Incidence was calculated per 100,000 population using 2018 U.S. Census population estimates for U.S. states and the District of Columbia obtained from CDC WONDER (https://wonder.cdc.gov/single-race-population.html).

** https://www.cdc.gov/coronavirus/2019-ncov/php/reporting-pui.html.

†† https://wwwn.cdc.gov/nndss; https://wwwn.cdc.gov/nndss/covid-19-response.html.

§§ According to the Council of State and Territorial Epidemiologists position statement Interim 20-ID-01, a probable case must 1) meet clinical criteria and epidemiologic criteria with no confirmatory laboratory testing performed; 2) have presumptive laboratory evidence, including detection of specific antigen or antibody in a clinical specimen, and meet clinical criteria or epidemiologic criteria; or 3) meet vital records criteria with no confirmatory laboratory testing performed. (https://cdn.ymaws.com/www.cste.org/resource/resmgr/2020ps/interim-20-id-01_covid-19.pdf)

¶¶ Cases reported from U.S. territories were not included in the analysis because of limited case reporting and lack of available demographically stratified census data. Cases excluded from this analysis include those reported from Guam (116), the Northern Mariana Islands (16), Puerto Rico (one), and the U.S. Virgin Islands (71).

<1%, 1%, and 55% of reports, respectively.*** Cases reported without sex or age data were excluded from this analysis as were cases meeting only the probable case definition, along with persons repatriated to the United States from Wuhan, China, or the Diamond Princess cruise ship. Cumulative incidence was estimated using 2018 population estimates. Because of the high prevalence of missing race and ethnicity data, estimates of incidence and proportions of underlying health conditions, symptoms, and severe outcomes by race and ethnicity were not described. Analyses are descriptive and statistical comparisons were not performed.

CDC received notification of the first case of laboratory-confirmed COVID-19 in the United States on January 22, 2020.††† As of May 30, an aggregate 1,761,503 U.S. COVID-19 cases and 103,700 deaths had been reported (Figure).§§§ The 7-day moving average number¶¶¶ of new daily cases peaked on April 12 (31,994) and deaths peaked on April 21 (2,856). As of May 30, the 7-day moving average numbers of new cases were 19,913 per day and deaths were 950 per day.

Among the 1,761,503 aggregate cases reported to CDC during January 22–May 30, individual case reports for 1,406,098 were submitted to CDC case surveillance. After exclusions, data for 1,320,488 (94%) cases were analyzed. Median age was 48 years (interquartile range = 33–63 years). Incidence was 403.6 cases per 100,000 population (Table 1) and was similar among females (406.0) and males (401.1).**** Incidence was higher among persons aged 40–49 years (541.6) and 50–59 years (550.5) than among those aged 60–69 years (478.4) and 70–79 years (464.2). Incidence was highest among persons aged ≥80 years (902.0)†††† and lowest among children aged ≤9 years (51.1). Among the 599,636 (45%) cases with information on both race and ethnicity, 36% of persons were non-Hispanic white, 33% were Hispanic, 22% were black, 4% were non-Hispanic Asian, 4% were non-Hispanic, other or multiple race, 1.3% were AI/AN, and <1% were non-Hispanic Native Hawaiian or other Pacific Islander.

Symptom status (symptomatic versus asymptomatic) was reported for 616,541 (47%) cases; among these, 22,007 (4%) were asymptomatic. Among 373,883 (28%) cases with data on individual symptoms, 70% noted fever, cough, or shortness of breath; 36% reported muscle aches, and 34% reported headache (Table 2). Overall, 31,191 (8%) persons reported loss of smell or taste.§§§§ Among patients aged ≥80 years, 60% reported fever, cough, or shortness of breath. No other symptoms were reported by >10% of persons in this age group.

Among 287,320 (22%) cases with data on individual underlying health conditions, those most frequently reported were cardiovascular disease (32%), diabetes (30%), and chronic lung disease (18%) (Table 2); the reported proportions were similar among males and females. The frequency of conditions reported varied by age group: cardiovascular disease was uncommon among those aged ≤39 years but was reported in approximately half of the cases among persons aged ≥70 years. Among 63,896 females aged 15–44 years with known pregnancy status, 6,708 (11%) were reported to be pregnant.

Among the 1,320,488 cases, outcomes for hospitalization, ICU admission, and death were available for 46%, 14%, and 36%, respectively. Overall, 184,673 (14%) patients were hospitalized, including 29,837 (2%) admitted to the ICU; 71,116 (5%) patients died (Table 3). Severe outcomes were more commonly reported for patients with reported underlying conditions. Hospitalizations were six times higher among patients with a reported underlying condition than those without reported underlying conditions (45.4% versus 7.6%). Deaths were 12 times higher among patients with reported underlying conditions compared with those without reported underlying conditions (19.5% versus 1.6%). The percentages of males who were hospitalized (16%), admitted to the ICU (3%), and who died (6%) were higher than were those for females (12%, 2%, and 5%, respectively). The percentage of ICU admissions was highest among persons with reported underlying conditions aged 60–69 years (11%) and 70–79 years (12%). Death was most commonly reported among persons aged ≥80 years regardless of the presence of underlying conditions (with underlying conditions 50%; without 30%).

Discussion

As of May 30, a total of 1,761,503 aggregate U.S. cases of COVID-19 and 103,700 associated deaths were reported to CDC. Although average daily reported cases and deaths are declining, 7-day moving averages of daily incidence of COVID-19 cases indicate ongoing community transmission.¶¶¶¶

*** Cases reported as Hispanic were categorized as "Hispanic or Latino persons of any race" regardless of availability of race data.

††† The first laboratory-confirmed case of COVID-19 in the United States was confirmed on January 20, 2020, and reported to CDC on January 22, 2020. The upper quartile of the lag between onset date and reporting to CDC was 15 days.

§§§ From April 15 to May 30, 2020, these aggregate counts include both confirmed and probable cases and deaths. Overall, <1% of cases and 3.1% of deaths were classified as probable.

¶¶¶ The 7-day moving average of new cases and deaths (current day + 6 preceding days / 7) was calculated to smooth expected variations in daily counts.

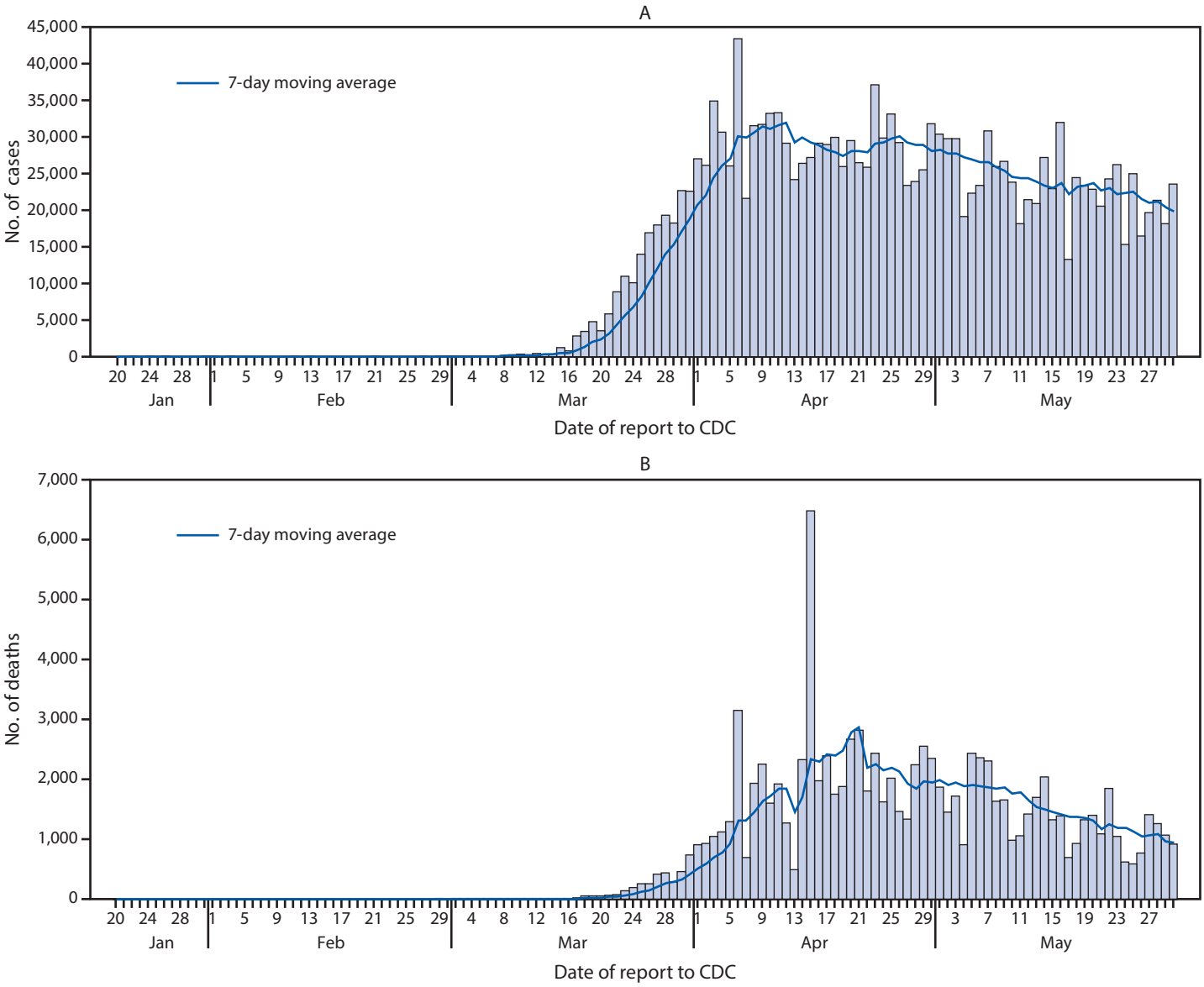
**** In some age groups, males had higher incidence, and in some age groups, females had higher incidence.

†††† Among those aged ≥85 years, incidence was 1,138 per 100,000.

§§§§ Responses include data from standardized fields supplemented with data from free-text fields; therefore, persons exhibiting this symptom might be underreported.

¶¶¶¶ Community transmission is defined by states and reflects varying conditions at the local and state levels.

FIGURE. Daily number of COVID-19 cases*,†,§,¶ (A) and COVID-19–associated deaths (B) reported to CDC — United States, January 22–May 30, 2020**



Abbreviation: COVID-19 = coronavirus disease 2019.

* From April 14, 2020, aggregate case counts reported by CDC included deaths attributable to both confirmed and probable COVID-19 as classified by reporting jurisdictions, using the Council of State and Territorial Epidemiologists position statement Interim-ID-20-01 (https://cdn.ymaws.com/www.cste.org/resource/resmgr/2020ps/interim-20-id-01_covid-19.pdf).

† The upper quartile of the lag between onset date and reporting to CDC was 15 days.

§ The daily number of deaths reported by jurisdictions on April 14 includes 4,141 deaths newly classified as probable.

¶ Overall <1% of cases reported in aggregate to CDC were classified as probable.

** Overall 3.1% of deaths reported in aggregate to CDC were classified as occuring in persons with probable cases.

The COVID-19 case data summarized here are essential statistics for the pandemic response and rely on information systems developed at the local, state, and federal level over decades for communicable disease surveillance that were rapidly adapted to meet an enormous, new public health threat. CDC aggregate counts are consistent with those presented through the Johns Hopkins University (JHU) Coronavirus Resource Center, which reported a cumulative total of 1,770,165 U.S. cases and 103,776 U.S. deaths on May 30, 2020.***** Differences in aggregate counts between CDC and

***** COVID-19 Dashboard by the Center for Systems Science and Engineering at Johns Hopkins University is a publicly available data tracker that extracts data from state, territorial, and local public health websites (https://coronavirus.jhu.edu/us-map). Data are archived in GitHub (https://github.com/CSSEGISandData/COVID-19/blob/master/csse_covid_19_data/csse_covid_19_daily_reports_us/05-30-2020.csv).

TABLE 1. Reported laboratory-confirmed COVID-19 cases and estimated cumulative incidence,* by sex† and age group — United States, January 22–May 30, 2020

	Males		Females		Total	
Age group (yrs)	No. (%)	Cumulative incidence*	No. (%)	Cumulative incidence*	No. (%)	Cumulative incidence*
0–9	10,743 (1.7)	52.5	9,715 (1.4)	49.7	20,458 (1.5)	51.1
10–19	24,302 (3.8)	113.4	24,943 (3.7)	121.4	49,245 (3.7)	117.3
20–29	85,913 (13.3)	370.0	96,556 (14.3)	434.6	182,469 (13.8)	401.6
30–39	108,319 (16.8)	492.8	106,530 (15.8)	490.5	214,849 (16.3)	491.6
40–49	109,745 (17.0)	547.0	109,394 (16.2)	536.2	219,139 (16.6)	541.6
50–59	119,152 (18.4)	568.8	116,622 (17.3)	533.0	235,774 (17.9)	550.5
60–69	93,596 (14.5)	526.9	85,411 (12.7)	434.6	179,007 (13.6)	478.4
70–79	53,194 (8.2)	513.7	52,058 (7.7)	422.7	105,252 (8.0)	464.2
≥80	41,394 (6.4)	842.0	72,901 (10.8)	940.0	114,295 (8.7)	902.0
All ages	**646,358 (100.0)**	**401.1**	**674,130 (100.0)**	**406.0**	**1,320,488 (100.0)**	**403.6**

Abbreviation: COVID-19 = coronavirus disease 2019.
* Per 100,000 population.
† The analytic dataset excludes cases reported through case surveillance that were missing information on sex (n = 19,918) or age (n = 2,379).

TABLE 2. Reported underlying health conditions* and symptoms† among persons with laboratory-confirmed COVID-19, by sex and age group — United States, January 22–May 30, 2020

	No. (%)											
		Sex		Age group (yrs)								
Characteristic	Total	Male	Female	≤9	10–19	20–29	30–39	40–49	50–59	60–69	70–79	≥80
Total population	**1,320,488**	**646,358**	**674,130**	**20,458**	**49,245**	**182,469**	**214,849**	**219,139**	**235,774**	**179,007**	**105,252**	**114,295**
Underlying health condition§												
Known underlying medical condition status*	**287,320 (21.8)**	138,887 (21.5)	148,433 (22.0)	2,896 (14.2)	7,123 (14.5)	27,436 (15.0)	33,483 (15.6)	40,572 (18.5)	54,717 (23.2)	50,125 (28.0)	34,400 (32.7)	36,568 (32.0)
Any cardiovascular disease¶	**92,546 (32.2)**	47,567 (34.2)	44,979 (30.3)	78 (2.7)	164 (2.3)	1,177 (4.3)	3,588 (10.7)	8,198 (20.2)	16,954 (31.0)	21,466 (42.8)	18,763 (54.5)	22,158 (60.6)
Any chronic lung disease	**50,148 (17.5)**	20,930 (15.1)	29,218 (19.7)	363 (12.5)	1,285 (18)	4,537 (16.5)	5,110 (15.3)	6,127 (15.1)	8,722 (15.9)	9,200 (18.4)	7,436 (21.6)	7,368 (20.1)
Renal disease	**21,908 (7.6)**	12,144 (8.7)	9,764 (6.6)	21 (0.7)	34 (0.5)	204 (0.7)	587 (1.8)	1,273 (3.1)	2,789 (5.1)	4,764 (9.5)	5,401 (15.7)	6,835 (18.7)
Diabetes	**86,737 (30.2)**	45,089 (32.5)	41,648 (28.1)	12 (0.4)	225 (3.2)	1,409 (5.1)	4,106 (12.3)	9,636 (23.8)	19,589 (35.8)	22,314 (44.5)	16,594 (48.2)	12,852 (35.1)
Liver disease	**3,953 (1.4)**	2,439 (1.8)	1,514 (1.0)	5 (0.2)	19 (0.3)	132 (0.5)	390 (1.2)	573 (1.4)	878 (1.6)	1,074 (2.1)	583 (1.7)	299 (0.8)
Immunocompromised	**15,265 (5.3)**	7,345 (5.3)	7,920 (5.3)	61 (2.1)	146 (2.0)	646 (2.4)	1,253 (3.7)	2,005 (4.9)	3,190 (5.8)	3,421 (6.8)	2,486 (7.2)	2,057 (5.6)
Neurologic/ Neurodevelopmental disability	**13,665 (4.8)**	6,193 (4.5)	7,472 (5.0)	41 (1.4)	113 (1.6)	395 (1.4)	533 (1.6)	734 (1.8)	1,338 (2.4)	2,006 (4.0)	2,759 (8.0)	5,746 (15.7)
Symptom§												
Known symptom status†	**373,883 (28.3)**	178,223 (27.6)	195,660 (29.0)	5,188 (25.4)	12,689 (25.8)	51,464 (28.2)	59,951 (27.9)	62,643 (28.6)	70,040 (29.7)	52,178 (29.1)	28,583 (27.2)	31,147 (27.3)
Fever, cough, or shortness of breath	**260,706 (69.7)**	125,768 (70.6)	134,938 (69.0)	3,278 (63.2)	7,584 (59.8)	35,072 (68.1)	42,016 (70.1)	45,361 (72.4)	51,283 (73.2)	37,701 (72.3)	19,583 (68.5)	18,828 (60.4)
Fever††	**161,071 (43.1)**	80,578 (45.2)	80,493 (41.1)	2,404 (46.3)	4,443 (35.0)	20,381 (39.6)	25,887 (43.2)	28,407 (45.3)	32,375 (46.2)	23,591 (45.2)	12,190 (42.6)	11,393 (36.6)
Cough	**187,953 (50.3)**	89,178 (50.0)	98,775 (50.5)	1,912 (36.9)	5,257 (41.4)	26,284 (51.1)	31,313 (52.2)	34,031 (54.3)	38,305 (54.7)	27,150 (52.0)	12,837 (44.9)	10,864 (34.9)
Shortness of breath	**106,387 (28.5)**	49,834 (28.0)	56,553 (28.9)	339 (6.5)	2,070 (16.3)	13,649 (26.5)	16,851 (28.1)	18,978 (30.3)	21,327 (30.4)	16,018 (30.7)	8,971 (31.4)	8,184 (26.3)
Myalgia	**135,026 (36.1)**	61,922 (34.7)	73,104 (37.4)	537 (10.4)	3,737 (29.5)	21,153 (41.1)	26,464 (44.1)	28,064 (44.8)	28,594 (40.8)	17,360 (33.3)	6,015 (21.0)	3,102 (10.0)
Runny nose	**22,710 (6.1)**	9,900 (5.6)	12,810 (6.5)	354 (6.8)	1,025 (8.1)	4,591 (8.9)	4,406 (7.3)	4,141 (6.6)	4,100 (5.9)	2,671 (5.1)	923 (3.2)	499 (1.6)
Sore throat	**74,840 (20.0)**	31,244 (17.5)	43,596 (22.3)	664 (12.8)	3,628 (28.6)	14,493 (28.2)	14,855 (24.8)	14,490 (23.1)	13,930 (19.9)	8,192 (15.7)	2,867 (10.0)	1,721 (5.5)
Headache	**128,560 (34.4)**	54,721 (30.7)	73,839 (37.7)	785 (15.1)	5,315 (41.9)	23,723 (46.1)	26,142 (43.6)	26,245 (41.9)	26,057 (37.2)	14,735 (28.2)	4,163 (14.6)	1,395 (4.5)
Nausea/Vomiting	**42,813 (11.5)**	16,549 (9.3)	26,264 (13.4)	506 (9.8)	1,314 (10.4)	6,648 (12.9)	7,661 (12.8)	8,091 (12.9)	8,737 (12.5)	5,953 (11.4)	2,380 (8.3)	1,523 (4.9)
Abdominal pain	**28,443 (7.6)**	11,553 (6.5)	16,890 (8.6)	349 (6.7)	978 (7.7)	4,211 (8.2)	5,150 (8.6)	5,531 (8.8)	6,134 (8.8)	3,809 (7.3)	1,449 (5.1)	832 (2.7)
Diarrhea	**72,039 (19.3)**	32,093 (18.0)	39,946 (20.4)	704 (13.6)	1,712 (13.5)	9,867 (19.2)	12,769 (21.3)	13,958 (22.3)	15,536 (22.2)	10,349 (19.8)	4,402 (15.4)	2,742 (8.8)
Loss of smell or taste	**31,191 (8.3)**	12,717 (7.1)	18,474 (9.4)	67 (1.3)	1,257 (9.9)	6,828 (13.3)	6,907 (11.5)	6,361 (10.2)	5,828 (8.3)	2,930 (5.6)	775 (2.7)	238 (0.8)

Abbreviation: COVID-19 = coronavirus disease 2019.
* Status of underlying health conditions known for 287,320 persons. Status was classified as "known" if any of the following conditions were reported as present or absent: diabetes mellitus, cardiovascular disease (including hypertension), severe obesity (body mass index ≥40 kg/m^2), chronic renal disease, chronic liver disease, chronic lung disease, immunocompromising condition, autoimmune condition, neurologic condition (including neurodevelopmental, intellectual, physical, visual, or hearing impairment), psychologic/psychiatric condition, and other underlying medical condition not otherwise specified.
† Symptom status was known for 373,883 persons. Status was classified as "known" if any of the following symptoms were reported as present or absent: fever (measured >100.4°F [38°C] or subjective), cough, shortness of breath, wheezing, difficulty breathing, chills, rigors, myalgia, rhinorrhea, sore throat, chest pain, nausea or vomiting, abdominal pain, headache, fatigue, diarrhea (≥3 loose stools in a 24-hour period), or other symptom not otherwise specified on the form.
§ Responses include data from standardized fields supplemented with data from free-text fields. Information for persons with loss of smell or taste was exclusively extracted from a free-text field; therefore, persons exhibiting this symptom were likely underreported.
¶ Includes persons with reported hypertension.
** Includes all persons with at least one of these symptoms reported.
†† Persons were considered to have a fever if information on either measured or subjective fever variables if "yes" was reported for either variable.

TABLE 3. Reported hospitalizations,*,† intensive care unit (ICU) admissions,§ and deaths¶ among laboratory-confirmed COVID-19 patients with and without reported underlying health conditions, by sex and age — United States, January 22–May 30, 2020**

	Outcome, no./total no. (%)††								
	Reported hospitalizations*,† (including ICU)			Reported ICU admission§			Reported deaths¶		
Characteristic (no.)	Among all patients	Among patients with reported underlying health conditions	Among patients with no reported underlying health conditions	Among all patients	Among patients with reported underlying health conditions	Among patients with no reported underlying health conditions	Among all patients	Among patients with reported underlying health conditions	Among patients with no reported underlying health conditions
Sex									
Male (646,358)	101,133/646,358 (15.6)	49,503/96,839 (51.1)	3,596/42,048 (8.6)	18,394/646,358 (2.8)	10,302/96,839 (10.6)	864/42,048 (2.1)	38,773/646,358 (6.0)	21,667/96,839 (22.4)	724/42,048 (1.7)
Female (674,130)	83,540/674,130 (12.4)	40,698/102,040 (39.9)	3,087/46,393 (6.7)	11,443/674,130 (1.7)	6,672/102,040 (6.5)	479/46,393 (1.0)	32,343/674,130 (4.8)	17,145/102,040 (16.8)	707/46,393 (1.5)
Age group (yrs)									
≤9 (20,458)	848/20,458 (4.1)	138/619 (22.3)	84/2,277 (3.7)	141/20,458 (0.7)	31/619 (5.0)	16/2,277 (0.7)	13/20,458 (0.1)	4/619 (0.6)	2/2,277 (0.1)
10–19 (49,245)	1,234/49,245 (2.5)	309/2,076 (14.9)	115/5,047 (2.3)	216/49,245 (0.4)	72/2,076 (3.5)	17/5,047 (0.3)	33/49,245 (0.1)	16/2,076 (0.8)	4/5,047 (0.1)
20–29 (182,469)	6,704/182,469 (3.7)	1,559/8,906 (17.5)	498/18,530 (2.7)	864/182,469 (0.5)	300/8,906 (3.4)	56/18,530 (0.3)	273/182,469 (0.1)	122/8,906 (1.4)	24/18,530 (0.1)
30–39 (214,849)	12,570/214,849 (5.9)	3,596/14,854 (24.2)	828/18,629 (4.4)	1,879/214,849 (0.9)	787/14,854 (5.3)	135/18,629 (0.7)	852/214,849 (0.4)	411/14,854 (2.8)	21/18,629 (0.1)
40–49 (219,139)	19,318/219,139 (8.8)	7,151/24,161 (29.6)	1,057/16,411 (6.4)	3,316/219,139 (1.5)	1,540/24,161 (6.4)	208/16,411 (1.3)	2,083/219,139 (1.0)	1,077/24,161 (4.5)	58/16,411 (0.4)
50–59 (235,774)	31,588/235,774 (13.4)	14,639/40,297 (36.3)	1,380/14,420 (9.6)	5,986/235,774 (2.5)	3,335/40,297 (8.3)	296/14,420 (2.1)	5,639/235,774 (2.4)	3,158/40,297 (7.8)	131/14,420 (0.9)
60–69 (179,007)	39,422/179,007 (22.0)	21,064/42,206 (49.9)	1,216/7,919 (15.4)	7,403/179,007 (4.1)	4,588/42,206 (10.9)	291/7,919 (3.7)	11,947/179,007 (6.7)	7,050/42,206 (16.7)	187/7,919 (2.4)
70–79 (105,252)	35,844/105,252 (34.1)	20,451/31,601 (64.7)	780/2,799 (27.9)	5,939/105,252 (5.6)	3,771/31,601 (11.9)	199/2,799 (7.1)	17,510/105,252 (16.6)	10,008/31,601 (31.7)	286/2,799 (10.2)
≥80 (114,295)	37,145/114,295 (32.5)	21,294/34,159 (62.3)	725/2,409 (30.1)	4,093/114,295 (3.6)	2,550/34,159 (7.5)	125/2,409 (5.2)	32,766/114,295 (28.7)	16,966/34,159 (49.7)	718/2,409 (29.8)
Total (1,320,488)	**184,673/1,320,488 (14.0)**	**90,201/198,879 (45.4)**	**6,683/88,441 (7.6)**	**29,837/1,320,488 (2.3)**	**16,974/198,879 (8.5)**	**1,343/88,441 (1.5)**	**71,116/1,320,488 (5.4)**	**38,812/198,879 (19.5)**	**1,431/88,441 (1.6)**

Abbreviation: COVID-19 = coronavirus disease 2019.

* Hospitalization status was known for 600,860 (46%). Among 184,673 hospitalized patients, the presence of underlying health conditions was known for 96,884 (53%).

† Includes reported ICU admissions.

§ ICU admission status was known for 186,563 (14%) patients among the total case population, representing 34% of hospitalized patients. Among 29,837 patients admitted to the ICU, the status of underlying health conditions was known for 18,317 (61%).

¶ Death outcomes were known for 480,565 (36%) patients. Among 71,116 reported deaths through case surveillance, the status of underlying health conditions was known for 40,243 (57%) patients.

** Status of underlying health conditions was known for 287,320 (22%) patients. Status was classified as "known" if any of the following conditions were noted as present or absent: diabetes mellitus, cardiovascular disease including hypertension, severe obesity body mass index ≥40 kg/m^2, chronic renal disease, chronic liver disease, chronic lung disease, any immunocompromising condition, any autoimmune condition, any neurologic condition including neurodevelopmental, intellectual, physical, visual, or hearing impairment, any psychologic/psychiatric condition, and any other underlying medical condition not otherwise specified.

†† Outcomes were calculated as the proportion of persons reported to be hospitalized, admitted to an ICU, or who died among total in the demographic group. Outcome underreporting could result from outcomes that occurred but were not reported through national case surveillance or through clinical progression to severe outcomes that occurred after time of report.

JHU might be attributable to differences in reporting practices to CDC and jurisdictional websites accessed by JHU.

Reported cumulative incidence in the case surveillance population among persons aged ≥20 years is notably higher than that among younger persons. The lower incidence in persons aged ≤19 years could be attributable to undiagnosed milder or asymptomatic illnesses among this age group that were not reported. Incidence in persons aged ≥80 years was nearly double that in persons aged 70–79 years.

Among cases with known race and ethnicity, 33% of persons were Hispanic, 22% were black, and 1.3% were AI/AN. These findings suggest that persons in these groups, who account for 18%, 13%, and 0.7% of the U.S. population, respectively, are disproportionately affected by the COVID-19 pandemic. The proportion of missing race and ethnicity data limits the conclusions that can be drawn from descriptive analyses; however, these findings are consistent with an analysis of COVID-19–Associated Hospitalization Surveillance Network (COVID-NET)††††† data that found higher proportions of black and Hispanic persons among hospitalized COVID-19 patients than were in the overall population (*4*). The completeness of race and ethnicity variables in case surveillance has increased from 20% to >40% from April 2 to June 2. Although reporting of race and ethnicity continues to improve, more complete data might be available in aggregate on jurisdictional websites or through sources like the COVID Tracking Project's COVID Racial Data Tracker.§§§§§

††††† COVID-Net is a population-based surveillance system that collects data on laboratory-confirmed COVID-19–associated hospitalizations (https://www.cdc.gov/coronavirus/2019-ncov/covid-data/covid-net/purpose-methods.html).

§§§§§ The COVID Tracking Project is *The Atlantic's* volunteer organization to collect and publish U.S. COVID-19 data (https://covidtracking.com/race/dashboard).

The data in this report show that the prevalence of reported symptoms varied by age group but was similar among males and females. Fewer than 5% of persons were reported to be asymptomatic when symptom data were submitted. Persons without symptoms might be less likely to be tested for COVID-19 because initial guidance recommended testing of only symptomatic persons and was hospital-based. Guidance on testing has evolved throughout the response.¶¶¶¶¶ Whereas incidence among males and females was similar overall, severe outcomes were more commonly reported among males. Prevalence of reported severe outcomes increased with age; the percentages of hospitalizations, ICU admissions, and deaths were highest among persons aged ≥70 years, regardless of underlying conditions, and lowest among those aged ≤19 years. Hospitalizations were six times higher and deaths 12 times higher among those with reported underlying conditions compared with those with none reported. These findings are consistent with previous reports that found that severe outcomes increased with age and underlying condition, and males were hospitalized at a higher rate than were females (*2*,*4*,*5*).

The findings in this report are subject to at least three limitations. First, case surveillance data represent a subset of the total cases of COVID-19 in the United States; not every case in the community is captured through testing and information collected might be limited if persons are unavailable or unwilling to participate in case investigations or if medical records are unavailable for data extraction. Reported cumulative incidence, although comparable across age and sex groups within the case surveillance population, are underestimates of the U.S. cumulative incidence of COVID-19. Second, reported frequencies of individual symptoms and underlying health conditions presented from case surveillance likely underestimate the true prevalence because of missing data. Finally, asymptomatic cases are not captured well in case surveillance. Asymptomatic persons are unlikely to seek testing unless they are identified through active screening (e.g., contact tracing), and, because of limitations in testing capacity and in accordance with guidance, investigation of symptomatic persons is prioritized. Increased identification and reporting of asymptomatic cases could affect patterns described in this report.

Similar to earlier reports on COVID-19 case surveillance, severe outcomes were more commonly reported among persons who were older and those with underlying health conditions (*1*). Findings in this report align with demographic and severe outcome trends identified through COVID-NET (*4*). Findings from case surveillance are evaluated along with enhanced surveillance data and serologic survey results to provide a comprehensive picture of COVID-19 trends, and differences in proportion of cases by racial and ethnic groups should continue to be examined in enhanced surveillance to better understand populations at highest risk.

¶¶¶¶¶ https://www.cdc.gov/coronavirus/2019-ncov/symptoms-testing/testing.html.

Summary

What is already known about this topic?

Surveillance data reported to CDC through April 2020 indicated that COVID-19 leads to severe outcomes in older adults and those with underlying health conditions.

What is added by this report?

As of May 30, 2020, among COVID-19 cases, the most common underlying health conditions were cardiovascular disease (32%), diabetes (30%), and chronic lung disease (18%). Hospitalizations were six times higher and deaths 12 times higher among those with reported underlying conditions compared with those with none reported.

What are the implications for public health practice?

Surveillance at all levels of government, and its continued modernization, is critical for monitoring COVID-19 trends and identifying groups at risk for infection and severe outcomes. These findings highlight the continued need for community mitigation strategies, especially for vulnerable populations, to slow COVID-19 transmission.

Since the U.S. COVID-19 response began in January, CDC has built on existing surveillance capacity to monitor the impact of illness nationally. Collection of detailed case data is a resource-intensive public health activity, regardless of disease incidence. The high incidence of COVID-19 has highlighted limitations of traditional public health case surveillance approaches to provide real-time intelligence and supports the need for continued innovation and modernization. Despite limitations, national case surveillance of COVID-19 serves a critical role in the U.S. COVID-19 response: these data demonstrate that the COVID-19 pandemic is an ongoing public health crisis in the United States that continues to affect all populations and result in severe outcomes including death. National case surveillance findings provide important information for targeted enhanced surveillance efforts and development of interventions critical to the U.S. COVID-19 response.

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Corresponding author: Erin K. Stokes, Estokes@cdc.gov, 404-718-1175.

[1]CDC COVID-19 Emergency Response.

All authors have completed and submitted the International Committee of Medical Journal Editors form for disclosure of potential conflicts of interest. No potential conflicts of interest were disclosed.

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EXHIBIT 3

DEPARTMENT OF HEALTH & HUMAN SERVICES
Centers for Medicare & Medicaid Services
7500 Security Boulevard, Mail Stop C2-21-16
Baltimore, Maryland 21244-1850

CENTERS FOR MEDICARE & MEDICAID SERVICES

Center for Clinical Standards and Quality/Quality, Safety & Oversight Group

Ref: QSO-20-13-Hospitals-*CAHs*
(REVISED)

DATE: **March 30, 2020**

TO: State Survey Agency Directors

FROM: Director
Quality, Safety & Oversight Group

SUBJECT: Guidance for Infection Control and Prevention *of* Coronavirus Disease (COVID-19) *in Hospitals, Psychiatric Hospitals, and Critical Access Hospitals (CAHs)*: FAQs, Considerations for Patient Triage, Placement, *Limits to Visitation and Availability of 1135 waivers.*

Memorandum Summary

- ***The Centers for Medicare & Medicaid Services (CMS) is committed*** to taking critical steps to ensure America's health care facilities and clinical laboratories are prepared to respond to the threat of the COVID-19.
- ***Coordination with the Centers for Disease Control (CDC) and local public health departments*** - We encourage all hospitals, *psychiatric hospitals, and CAHs* to monitor the CDC website for information and resources and contact their local health department when needed (CDC Resources for Health Care Facilities: https://www.cdc.gov/coronavirus/2019-ncov/healthcare-facilities/index.html).
- ***Hospital/CAH Guidance and Actions*** - CMS regulations and guidance support hospitals *and CAHs* taking appropriate action to address potential and confirmed COVID-19 cases to mitigate transmission *and prepare for community spread* transmission, including screening, discharge and transfers from the hospital, *mitigation of staffing crises,* and visitation.
- ***Hospital/CAH Flexibilities*** – *Under Section 1135 of the Social Security Act (Act), CMS has waived a number of hospital/CAH requirements following the President's declaration of a national state of emergency and the Secretary's declaration of a Public Health Emergency to facilitate increasing hospital capacity, establishing alternate care sites, and removing administrative burdens.*

Background

CMS is committed to the protection of patients and residents of healthcare facilities from the spread of infectious disease. This memorandum responds to questions we have received and provides important guidance for hospitals, *psychiatric hospitals*, and critical access hospitals (CAHs) in addressing the COVID-19 outbreak and minimizing transmission to other

individuals. Specifically, we address FAQs related to optimizing patient placement, with the goal of addressing the needs of the individual patient while protecting other patients and healthcare workers.

Guidance

Hospitals*, psychiatric hospitals, and CAHs* should monitor the Centers for Disease Control and Prevention's (CDC) website (https://www.cdc.gov/coronavirus/2019-nCoV/hcp/index.html) for up-to-date information and resources *for the mitigation of transmission of COVID-19 for both inpatient and outpatient facilities.* They should contact their local health department if they have questions or suspect a patient or healthcare provider has COVID-19. Hospitals*, psychiatric hospitals, and CAHs* should have plans for monitoring healthcare personnel with exposure to patients with known or suspected COVID-19. Also, in light of limited staffing options, there should be a plan for how exposed or infected healthcare personnel may return to work. Additional information about monitoring healthcare personnel *and returning to work* is available here: https://www.cdc.gov/coronavirus/2019-ncov/hcp/guidance-risk-assesment-hcp.html; https://www.cdc.gov/coronavirus/2019-ncov/healthcare-facilities/hcp-return-work.html

Hospital, Psychiatric Hospital, and CAH Capacity for Acute Inpatient Care and Excluded Psychiatric and Rehabilitation Units

CMS has waived a number of requirements under Section 1135 for all hospitals including CAHs and psychiatric hospitals. Current information on 1135 waivers available to all hospitals/CAHs and psychiatric hospitals can be found at: https://www.cms.gov/files/document/covid19-emergency-declaration-health-care-providers-fact-sheet.pdf and https://www.cms.gov/About-CMS/Agency-Information/Emergency/EPRO/Current-Emergencies/Current-Emergencies-page

Case-by-case waivers may be requested at 1135waiver@cms.hhs.gov.

Guidance for *Mitigating Transmission and Preparing for Community Spread* of COVID-19 Addressing Patient Triage, Placement of Patients with known or suspected COVID-19, *Mitigation of Staffing Shortages (due to COVID-19 patient surges and/or staff becoming infected) and Expanded Visitation Recommendations*

If healthcare personnel have been exposed or infected with COVID-19, when can they return to work to prevent staffing shortages?

According to CDC, in hospitals where testing is available, it is suggested that test-based strategies are preferred.

1. *Test-based strategy. Personnel should be excluded from work until:*

    - *Resolution of fever without the use of fever-reducing medications,* ***and***
    - *Improvement in respiratory symptoms (e.g., cough, shortness of breath),* ***and***
    - *Negative results of an FDA Emergency Use Authorized molecular assay for COVID-19 from at least two consecutive nasopharyngeal swab specimens collected ≥24 hours apart (total of two negative specimens)[1]. See Interim Guidelines for Collecting, Handling, and Testing Clinical Specimens for 2019 Novel Coronavirus (2019-nCoV).*

2. *Non-test-based strategy. Personnel should be excluded from work until:*

    - *At least 3 days (72 hours) have passed since recovery, defined as resolution of fever without the use of fever-reducing medications **and** improvement in respiratory symptoms (e.g., cough, shortness of breath); **and**,*
    - *At least 7 days have passed since symptoms first appeared.*

If healthcare personnel were never tested for COVID-19 but have an alternate diagnosis such has having tested positive for influenza, criteria for return to work should be based on existing guidance for that diagnosis.

Are there special considerations for previously exposed or infected healthcare personnel when returning to the workplace?

Before returning to work, exposed healthcare personnel should:

- *Consult with their occupational health program, be monitored for symptoms, and seek re-evaluation from occupational health if fever and/or respiratory symptoms recur or worsen.*

For more information on self-monitoring please see: https://www.cdc.gov/coronavirus/2019-ncov/hcp/guidance-risk-assesment-hcp.html

Healthcare personnel with confirmed or suspected COVID-19 should consult with their occupational health program and follow the CDC Interim guidance on return to work. https://www.cdc.gov/coronavirus/2019-ncov/healthcare-facilities/hcp-return-work.html

What additional measures should a hospital, psychiatric hospital, or CAH consider for the mitigation of transmission in outpatient settings?

- *Reschedule non-urgent outpatient visits as necessary.*
- *Consider reaching out to patients who may be at a higher risk of COVID-19-related complications such as the elderly, those with medical co-morbidities, and potentially other persons who are at higher risk for complications from respiratory diseases, such as pregnant women to ensure adherence to current medications and therapeutic regimens, confirm they have sufficient medication refills, and provide instructions to notify their provider by phone if they become ill.*
- *Consider accelerating the timing of high priority screening and intervention needs for the short-term, in anticipation of the possible need to manage an influx of COVID-19 patients in the weeks to come.*
- *Symptomatic patients who need to be seen in a clinical setting should be asked to call before they leave home, so staff are ready to receive them using appropriate infection control practices, including providing a mask for the potentially infectious patient before or immediately upon entry into the healthcare facility, and personal protective equipment for the healthcare personnel.*

What additional measures should a hospital, psychiatric hospital or CAH consider for the mitigation of transmission in inpatient settings?

- *Reschedule elective surgeries, procedures, and other visits as necessary.*

- *Shift elective urgent inpatient diagnostic and surgical procedures to outpatient settings, when feasible.*
- *Maintain social distancing of at least six feet during group therapy interactions.*
- *Limit visitors to COVID-19 positive patients and persons under investigation (PUI).*
- *Plan for a surge of critically ill patients and identify additional space to care for these patients. Include options for:*
    - *Using alternate and separate spaces in the ER, ICUs, and other patient care areas to manage known or suspected COVID-19 patients.*
    - *Separating known or suspected COVID-19 patients from other patients ("cohorting").*
    - *Identifying dedicated staff to care for COVID-19 patients.*

Can an acute care inpatient be admitted to an excluded psychiatric unit to temporarily expand bed capacity?

Yes, CMS will allow acute care hospitals/CAHs with excluded distinct part psychiatric units that need to relocate acute care inpatients to excluded distinct part psychiatric units to provide care for overflow due to COVID-19 patients.

Can an acute care inpatient be admitted to an excluded rehabilitation unit to temporarily expand bed capacity?

Yes, CMS will allow acute care hospitals/CAHs with excluded distinct part inpatient rehabilitation units that need to relocate acute care inpatients to excluded distinct part rehabilitation units in order to provide care for overflow due to COVID-19 patients. The distinct part unit's bed must be appropriate for the acute care inpatient.

Can an inpatient of an excluded rehabilitation unit be admitted to an acute care inpatient unit to temporarily expand bed capacity?

Yes, CMS will allow acute care hospitals/CAHs with excluded distinct part inpatient rehabilitation units that relocate their inpatients to an acute care bed and unit units to provide care for overflow due to COVID-19 patients. This waiver may be utilized where the hospital/CAH's acute care beds are appropriate for providing care to rehabilitation patients and such patients continue to receive intensive rehabilitation services.

Can an excluded unit psychiatric inpatient be admitted to an acute care inpatient unit to expand bed capacity?

Yes, CMS will allow acute care hospitals/CAHs with excluded distinct part inpatient psychiatric units to relocate their inpatients to an acute care bed and unit to provide care for overflow due to COVID-19 patients. This waiver may be used when the hospital/CAH's acute care beds are appropriate for psychiatric patients and the staff and environment are conducive to safe care. For psychiatric patients, this includes assessment of the acute care bed and unit location to ensure those patients at risk of harm to self and others receive safe and appropriate care.

Which patients are at risk for severe disease for COVID-19?

Based upon CDC data *https://www.cdc.gov/coronavirus/2019-ncov/specific-groups/high-risk-complications.html*, older adults and those with underlying chronic medical conditions or immunocompromised state may be most at risk for severe outcomes. This should be considered in the decision to monitor the patient as an outpatient or inpatient.

How should facilities screen visitors and patients for COVID-19?

Hospitals*, psychiatric hospitals, and CAHs* should identify visitors and patients at risk for having COVID-19 infection before or immediately upon arrival to the healthcare facility. They should ask patients about the following:

1. *Signs or symptoms of a respiratory infection, such as a fever, cough, or difficulty breathing.*
2. *Contact with a person who is positive for COVID-19 or with someone who is considered a PUI or someone who is ill with respiratory illness.*
3. *Travel within the last 14 days to areas with widespread or ongoing COVID-19 community spread. For updated information on countries and restricted areas within the U.S., visit: https://www.cdc.gov/coronavirus/2019-ncov/travelers/after-travel-precautions.html.*
4. *Residence or working in a community where community-based spread of COVID-19 is occurring. For more information on mitigation plans for communities identified to be at risk, visit: https://www.cdc.gov/coronavirus/2019-ncov/community/index.html.*

For patients, implement respiratory hygiene and cough etiquette (i.e., placing a facemask over the patient's nose and mouth if that has not already been done) and isolate the patient in an examination room with the door closed. If the patient cannot be immediately moved to an examination room, ensure they are not allowed to wait among other patients seeking care. Identify a separate, well-ventilated space that allows waiting patients to be separated by 6 or more feet, with easy access to respiratory hygiene supplies. In some settings, medically-stable patients might opt to wait in a personal vehicle or outside the healthcare facility where they can be contacted by mobile phone when it is their turn to be evaluated.

Inform infection prevention and control services, local and state public health authorities, and other healthcare facility staff as appropriate about the presence of a person under investigation for COVID-19. Additional guidance for evaluating patients in U.S. for COVID-19 infection can be found on the CDC COVID-19 website. *For more specific guidance see resource links*.

Provide supplies for respiratory hygiene and cough etiquette, including 60%-95% alcohol-based hand sanitizer (ABHS), tissues, no touch receptacles for disposal, facemasks, and tissues at healthcare facility entrances, waiting rooms, patient check-ins, etc.

How should facilities monitor or restrict healthcare facility staff?

The same screening performed for visitors should be performed for hospital*, psychiatric hospital, and CAH* staff.

- Healthcare providers (HCP) who have signs and symptoms of a respiratory infection should not report to work.
- Any staff that develop signs and symptoms of a respiratory infection while on-the-job, should:

- Immediately stop work, put on a facemask, and self-isolate at home.
- Inform the hospital*, psychiatric hospital, or CAH*'s infection *control professional/*preventionist and include information on individuals, equipment, and locations the person came in contact with.
- Contact and follow the local health department recommendations for next steps such as testing and locations for treatment.

- Refer to the CDC guidance for exposures that might warrant restricting asymptomatic healthcare personnel from reporting to work (https://www.cdc.gov/coronavirus/2019-ncov/hcp/guidance-risk-assesment-hcp.html).
- *Report cases of illness to their supervisor, employee health service, and/or occupational health clinic. Employees should also consult their healthcare provider if they are experiencing signs/symptoms consistent with COVID-19*

Hospitals*, psychiatric hospitals, and CAHs* should contact their local health department for questions, and frequently review the CDC website dedicated to COVID-19 for health care professionals (https://www.cdc.gov/coronavirus/2019-nCoV/hcp/index.html).

Can hospitals continue to procure organs for organ donation?

Yes. Ensuring that individuals have continued access to life-saving organs is critical. We understand that hospitals are preparing for a surge in COVID-19 patients; however, we would ask that donor hospitals continue with normal operations in regards to allowing organ procurement coordinators into hospitals to discuss organ donation with families wherever possible. Hospital and Organ Procurement Organization (OPO) leadership should communicate on risk assessments in their communities and any potential impacts for organ recovery operations.

What are recommended infection prevention and control practices, including considerations for patient placement, when evaluating and care for patients with known or suspected COVID-19?

Recommendations for patient placement and other detailed infection prevention and control recommendations regarding hand hygiene, Transmission-Based Precautions, environmental cleaning and disinfection, managing visitors, and monitoring and managing healthcare personnel are available in the CDC Interim Infection Prevention and Control Recommendations for Patients with Confirmed Coronavirus Disease 2019 (COVID-19) or Persons under Investigation for COVID-19 in Healthcare Settings.

Do all patients with known or suspected COVID-19 infection require hospitalization?

No. Patients may not require hospitalization and can be managed at home if they are able to comply with monitoring requests. More information is available here: https://www.cdc.gov/coronavirus/2019-ncov/hcp/guidance-home-care.html

Are there specific considerations for patients requiring diagnostic or therapeutic interventions?

Patients with known or suspected COVID-19 should continue to receive the intervention appropriate for the severity of their illness and overall clinical condition. Because some

procedures such as intubation create high risks for transmission additional precautions include: 1) HCP should wear all recommended *personal protective equipment (PPE),* 2) the number of HCP present should be limited to essential personnel, and 3) the room should be cleaned and disinfected in accordance with environmental infection control guidelines.

Additional information about performing aerosol-generating procedures is available here: https://www.cdc.gov/coronavirus/2019-ncov/infection-control/control-recommendations.html

Please note that CDC has issued updated strategies for optimizing the use of facemasks. https://www.cdc.gov/coronavirus/2019-ncov/hcp/ppe-strategy/face-masks.html.

When is it safe to discontinue Transmission-Based Precautions for hospitalized patients with COVID-19?

The decision to discontinue Transmission-Based Precautions for hospitalized patients with COVID-19 should be made on a case-by-case basis in consultation with clinicians, infection prevention and control specialists, and public health officials. This decision should consider disease severity, illness signs and symptoms, and results of laboratory testing for COVID-19 in respiratory specimens. More detailed information about criteria to discontinue Transmission-Based Precautions are available here: https://www.cdc.gov/coronavirus/2019-ncov/hcp/disposition-hospitalized- patients.html.

What are the considerations for discharge to a subsequent care location for patients with COVID-19?

The decision to discharge a patient from the hospital*, psychiatric hospital, or CAH* should be made based on the clinical condition of the patient. If Transmission-Based Precautions must be continued in the subsequent setting, the receiving facility must be able to implement all recommended infection prevention and control recommendations.

Although COVID-19 patients with mild symptoms may be managed at home, the decision to discharge to home should consider the patient's ability to adhere to isolation recommendations, as well as the potential risk of secondary transmission to household members with immunocompromising conditions. *Special consideration should be given to patients with psychiatric or cognitive disabilities to ensure they are able to adhere to the COVID-19 discharge recommendations and fully comprehend the significance of the precautions, or they have a family member or significant other involved to assist with these restrictions.* More information is available here: https://www.cdc.gov/coronavirus/2019-ncov/hcp/guidance-home-care.html

What are the implications of the Medicare Hospital*, psychiatric hospital, Psychiatric Hospital, and CAH* Discharge Planning Regulations for Patients with COVID-19?

Medicare's Discharge Planning Regulations (which were updated in November 2019) require that *the* hospital*, psychiatric hospital, or CAH* assess the patient's needs for post-hospital*, psychiatric hospital or CAH* services, and the availability of such services. When a patient is discharged, all necessary medical information (including communicable diseases) must be provided to any post-

acute service provider. For COVID-19 patients, this must be communicated to the receiving service provider prior to the discharge/transfer and to the healthcare transport personnel.

Can hospitals*, psychiatric hospital, and CAHs* restrict visitation of patients?

Medicare regulations require a hospital*, psychiatric hospital, or CAH* to have written policies and procedures regarding the visitation rights of patients, including those setting forth any clinically necessary or reasonable restriction or limitation that the hospital*, psychiatric hospital, or CAH* may need to place on such rights and the reasons for the clinical restriction or limitation. CMS sub-regulatory guidance identifies infection control concern as an example of when clinical restrictions may be warranted. Patients must be informed of his/her visitation rights and the clinical restrictions or limitations on visitation.

The development of such policies and procedures require hospitals to focus efforts on preventing and controlling infections, not just between patients and personnel, but also between individuals across the entire hospital*, psychiatric hospital, and CAH* setting (for example, among patients, staff, and visitors) as well as between the hospital*, psychiatric hospital, and CAH* and other healthcare institutions and settings and between patients and the healthcare environment. Hospitals*, psychiatric hospitals, and CAHs* should work with their local, state, and federal public health agencies to develop appropriate preparedness and response strategies for communicable disease threats.

Limiting visitors and individuals: Expanded recommendations:

CMS is providing the following expanded guidance for hospitals, psychiatric hospitals, and CAHs located in States with COVID-19 cases are present to prevent the spread of COVID-19:

a) *Visitors should receive the same screening as patients, including whether they have had:*
   - *Fever or symptoms of a respiratory infection, such as a cough and difficulty breathing.*
   - *International travel within the last 14 days to CDC Level 3 risk countries. For updated information on restricted countries visit: https://www.cdc.gov/coronavirus/2019-ncov/travelers/index.html and for considerations after recent international travel visit: https://www.cdc.gov/coronavirus/2019-ncov/travelers/after-travel-precautions.html*
   - *Recent trips (within the last 30 days) on cruise ships. For updated information on recent cruise ship travel, visit the CDC website: https://wwwnc.cdc.gov/travel/page/covid-19-cruise-ship*
   - *Contact with someone with known or suspected COVID-19 or ill with respiratory illness.*
   - *Travel in the last 14 days within the United States to restricted areas. Information and guidance on restricted areas within the US, visit: https://www.cdc.gov/coronavirus/2019-ncov/travelers/travel-in-the-us.html*

b) *Healthcare facilities should set limitations on visitation. For example, limitations may include restricting the number of visitors per patient, or limiting visitors to only those that provide assistance to the patient, or limiting visitors under a certain age.*

c) *Facilities must ensure patients have adequate and lawful access to chaplains or clergy in conformance with the Religious Freedom Restoration Act and Religious Land Use and Institutionalized Persons Act.*

d) *Healthcare facilities should provide signage at entrances for screening individuals, provide temperature checks/ ask about fever, and encourage frequent hand washing and use of hand sanitizer before entering the facility and before and after entering patient rooms*

e) If visiting and not seeking medical treatment themselves, individuals with fevers, cough, difficulty breathing, body aches or runny nose or those who are not following infection control guidance should be restricted from entry.

f) Facilities should instruct visitors to limit their movement within the facility by reducing such things as walking the halls or trips to the cafeteria.

g) Facilities should establish limited entry points for all visitors and/or establish alternative sites for screening prior to entry.

h) Facilities can implement measures to:

- *Increase communication with families (phone, social media, etc.)*
- *Potentially offer a hotline with a recording that is updated at set times so families can stay current on the facility's general status.*
- *If appropriate, consider offering telephonic screening of recent travel and wellness prior to coming in for scheduled appointments. This may help limit the amount of visitor movement throughout the organization and congestion at entry points.*

i) Consider closing common visiting areas and encouraging patients to visit with loved ones in their patient rooms.

CDC Resources:

- *Coronavirus Disease 2019 (COVID-19) Hospital Preparedness Assessment Tool https://www.cdc.gov/coronavirus/2019-ncov/hcp/hcp-hospital-checklist.html*
- CDC Resources for Health Care Facilities: https://www.cdc.gov/coronavirus/2019-ncov/healthcare-facilities/index.html
- CDC Updates: https://www.cdc.gov/coronavirus/2019-ncov/whats-new-all.html
- CDC FAQ for COVID-19**:** https://www.cdc.gov/coronavirus/2019-ncov/infection-control/infection-prevention-control-faq.html
- CDC Interim Infection Prevention and Control Recommendations for Patients with Confirmed Coronavirus Disease 2019 (COVID19) or Persons Under Investigation for COVID-19 in Healthcare Settings.: https://www.cdc.gov/coronavirus/2019-ncov/infection- control/controrecommendations.html?CDC_AA_refVal=. https%3A%2F%2Fwww.c dc.gov%2Fcoronavirus%2F2019-ncov%2Fhcp%2Finfection-control.html
- Health Department Directories: https://www.naccho.org/membership/lhd-directory

CDC Updates:

https://www.cdc.gov/coronavirus/2019-ncov/whats-new-all.html

Mental Health Resources:

SAMHSA has developed guidelines for Psychiatric Hospitals which can be found here: https://www.samhsa.gov/sites/default/files/covid19-interim-considerations-for-state-psychiatric-hospitals.pdf

CMS Resources:

CMS has additional guidance which may be beneficial to hospitals*, psychiatric hospitals, and*

CAHs related to *screening patients for COVID in alternate locations, Emergency Medical Treatment and Labor Act (EMTALA)* requirements and other topics surrounding the health and safety standards during emergencies: *https://www.cms.gov/files/document/qso-20-15-hospitalcahemtala.pdf.*

The document Provider Survey and Certification Frequently Asked Questions (FAQs), Declared Public Health Emergency All-Hazards are located at https://www.cms.gov/Medicare/Provider-Enrollment-and-Certification/SurveyCertEmergPrep/Downloads/All-Hazards-FAQs.pdf. These FAQs are not limited to situations involving 1135 Waivers, but are all encompassing FAQs related to public health emergencies and survey activities and functions.

Contact:

Questions about this memorandum should be addressed to QSOG_EmergencyPrep@cms.hhs.gov. Questions about COVID-19 guidance/screening criteria should be addressed to the State Epidemiologist or other responsible state or local public healt/h officials in your state.

Effective Date:

Immediately. This policy should be communicated with all survey and certification staff, their managers and the State/Regional Office training coordinators immediately.

/s/
David R. Wright

cc: Survey and Operations Group Management

EXHIBIT 4

DEPARTMENT OF HEALTH & HUMAN SERVICES
Centers for Medicare & Medicaid Services
7500 Security Boulevard, Mail Stop C2-21-16
Baltimore, Maryland 21244-1850

CENTERS FOR MEDICARE & MEDICAID SERVICES

Center for Clinical Standards and Quality/Quality, Safety & Oversight Group

Ref: QSO-20-23-ICF/IID & PRTF

DATE: **March 30, 2020**

TO: State Survey Agency Directors

FROM: Director
Quality, Safety & Oversight Group

SUBJECT: Guidance for Infection Control and Prevention of Coronavirus Disease 2019 (COVID-19) in Intermediate Care Facilities for Individuals with Intellectual Disabilities (ICF/IIDs) and Psychiatric Residential Treatment Facilities (PRTFs)

Memorandum Summary

- ***CMS is committed*** to taking critical steps to ensure America's health care facilities and clinical laboratories are prepared to respond to the threat of the COVID-19.
- **Guidance for Infection Control and Prevention of COVID-19 -** CMS is providing additional guidance to intermediate care facilities for individuals with intellectual disabilities (ICF/IIDs) to help them improve their infection control and prevention practices to prevent the transmission of COVID-19, including revised guidance for visitation.
- **Coordination with the Centers for Disease Control (CDC) and public health departments -** We encourage all ICF/IIDs and Psychiatric Residential Treatment Facilities (PRTFs) to monitor the CDC website for information and resources and contact their health department when needed (CDC Resources for Health Care Facilities: https://www.cdc.gov/coronavirus/2019- ncov/healthcare-facilities/index.html).

Background

CMS is responsible for ensuring the health and safety of ICF/IID and PRTF clients/residents by enforcing the standards required to help each client/resident attain or maintain their highest level of well-being. In light of the recent spread of COVID-19, we are providing additional guidance to ICF/IIDs and PRTFs to help control and prevent the spread of the virus SARS-CoV-2 and the disease it causes, COVID-19.

Guidance

Facility staff should regularly monitor the CDC website for information and resources (https://www.cdc.gov/coronavirus/2019-ncov/index.html). They should contact their state

health agency if they have questions or suspect a client/resident of an ICF/IID or PRTF has COVID-19. Per CDC, prompt detection, triage and isolation of potentially infectious clients/residents are essential to prevent unnecessary exposures among clients/residents, healthcare personnel, and visitors at the facility. Therefore, facilities should continue to be vigilant in identifying any possible infected individuals. Facilities should consider frequent monitoring for potential symptoms of respiratory infection as needed throughout the day. The following link can be used for guidance on screening visitors and monitoring or restricting facility health care staff: https://www.cdc.gov/coronavirus/2019-ncov/symptoms-testing/index.html.

Furthermore, we encourage facilities to take advantage of resources that have been made available by CDC and CMS to train and prepare staff to improve infection control and prevention practices See CDC and CMS resource links: https://www.cdc.gov/longtermcare/index.html and https://www.medicaid.gov/state-resource-center/disaster-response-toolkit/federal-disaster-resources/index.html. Lastly, facilities should maintain a person-centered approach to care. This includes communicating effectively with clients/residents, client/resident representatives and/or their family, and understanding their individual needs and goals of care. Staff should adjust communication about the COVID-19 disease and the underlying virus and SARS-CoV-2 infection prevention and control procedures being taken by the facility, and any potential modifications or restrictions to clients/residents' daily routine as appropriate to the client/resident/family member's age and preferred language, as well as their, emotional, psychological, and functioning status while using required auxiliary aides and services. Communications should not be limited based on an individual's functioning level; clients/residents should receive information regardless of functioning level.

Facilities experiencing any new respiratory illnesses (regardless of suspected etiology) among clients/residents or healthcare personnel should be initially evaluated by their facility medical professional and if deemed necessary contact their state health agency for further guidance. For information on your state's health agency link: https://www.cdc.gov/publichealthgateway/healthdirectories/healthdepartments.html.

Guidance for Limiting the Transmission of COVID-19 for ICF/IIDs and PRTFs

What flexibilities to the current regulations are available to ICF/IID and PRTF providers?

Response: President Trump's declaration of a national emergency due to COVID-19 was announced on Friday, March 13, 2020 which led to the Secretary of the Department of Health and Human Services to authorize CMS to take proactive steps through emergency waivers and modifications under section 1135 of the Social Security Act (Act) and rapidly expand the Administration's aggressive efforts against COVID-19. As a result of this authority, CMS will issue blanket waivers of certain requirements and will review other individual waiver requests on a case by case basis, which will ease certain requirements for impacted providers.

How do waivers & flexibilities help?

Response: We will use the allowable flexibilities and issue waivers as needed to help those affected by an emergency or disaster. If needed, specific waivers may be retroactive to the beginning of the emergency or disaster. We can also adjust some agency policies or procedures, usually without reprogramming our systems. Additional information is available at: https://www.cms.gov/About-

CMS/Agency-Information/Emergency/EPRO/Current-Emergencies/Current-Emergencies-page

What are blanket waivers?

Response: Under Section 1135 of the Act, CMS can implement specific waivers or modifications on a "blanket" basis when a determination has been made that all similarly situated providers in the emergency area need such a waiver or modification. When a blanket waiver is issued, providers do not have to apply for an individual waiver. Blanket waivers prevent access to care gaps for beneficiaries affected by the emergency. If there is no blanket waiver in place for a specific requirement, providers can ask for an individual Section 1135 waiver by following our instructions. In addition to 1135 waivers, we may also cover certain extended care services on an emergency basis under section 1812(f) of the Social Security Act.

Has CMS issued any 1135 waivers for ICF/IID or PRTF facilities?

Response: Current information about blanket waivers are available on the CMS website at:https://www.cms.gov/files/document/covid19-emergency-declaration-health-care-providers-fact-sheet.pdf. In addition, individual case-by-case waivers may be available by submitting a request to 1135waiver@cms.hhs.gov.

In cases where ICF/IID staffing is impacted by COVID-19, will CMS temporarily waive the minimum staffing requirements for ICF/IIDs?

Response: We encourage both ICF/IID and PRTF providers to review any state licensing requirements and work with their States on flexibilities to those requirements.

As described above, an emergency waiver under section 1135 can be requested, but otherwise CMS is not waiving ICF/IID staffing requirements. Please see https://www.cms.gov/About-CMS/Agency-Information/Emergency/EPRO/Current-Emergencies/Current-Emergencies-page for the latest information on 1135 waivers specific to specific health care providers. For case-specific waivers, the facility administrator or designated representative should submit your request to 1135waiver@cms.hhs.gov.

Can ICF/IIDs combine residents of several homes if staffing is not available? If so, do ICF/IIDs need to get a facility-specific authorization to exceed their certified bed capacity?

Response: Because of the high infection rate of COVID-19 and the increased vulnerability of people with disabilities to have serious response due to complications, people should, as a rule, not be forced into settings that would increase social interaction beyond recommended levels. Instead, people should be moved into community based settings and states should take advantage of the many opportunities for addressing staffing shortages. However, for ICF/IIDs that have multiple sites under a single CMS certification number, there is flexibility in cohorting residents for purposes of mitigating transmission. We would encourage consultation with state public health agencies to address combining facilities and staffing.

For separately-certified ICF/IIDs that need to combine, they should reach out to their State to address any state licensure requirements and may also seek specific 1135 emergency waivers. In all cases, ICF/IIDs should keep clear records of individuals who are moved, and should take appropriate measures to ensure the health and safety of those individuals during transit as well as at

the new location. If ICF/IIDs determine it is in the best interest of their residents to combine facilities, they should work to minimize the impact to residents (for example, by permitting residents to bring favorite possessions, clothes, etc.). For additional information on 1135 waivers, please see the links below.

If a State is not currently broadly testing for the coronavirus, we are aware of people who have symptoms, who have tested negative for both the flu and for RSV and who have been told by their healthcare provider to go home and not get anyone else sick because the provider does not have access to the test. At what point does the facility implement exposure measures and at what point do they contact the health department and CDC in this kind of scenario?

Response: The ICF/IID should follow the guidance of their State public health department or agency, the CDC and the CMS if they have additional concerns regarding client and staff exposure. See the following links:
https://www.cdc.gov/publichealthgateway/healthdirectories/healthdepartments.html,
https://www.cdc.gov/coronavirus/2019-ncov/symptoms-testing/index.html and
https://www.medicaid.gov/state-resource-center/disaster-response-toolkit/federal-disaster-resources/index.html .

How should facilities monitor or restrict health care facility staff?

Response: The same screening performed for visitors should be performed for facility staff.

- Health care providers (HCPs) who have signs and symptoms of a respiratory infection should not report to work.
- Any staff that develop signs and symptoms of a respiratory infection while on-the-job, should:
  - Immediately stop work, put on a facemask, and self-isolate at home;
  - Inform the facility's leadership, and include information on individuals, equipment, and locations the person came in contact with; and
  - Contact and follow the state health agency recommendations for next steps (e.g., testing).
- Refer to the CDC guidance for exposures that might warrant restricting asymptomatic healthcare personnel from reporting to work (https://www.cdc.gov/coronavirus/2019-ncov/hcp/guidance-risk-assesment-hcp.html).

Facilities should contact their state health agency for questions, and frequently review the CDC website dedicated to COVID-19 for health care professionals (https://www.cdc.gov/coronavirus/2019-nCoV/hcp/index.html).

Should ICF/IID community activities be limited in counties with confirmed COVID-19 cases for all people or should it be a person-centered decision based on the team's evaluation of the risks?

Response: Community activities should be limited in accordance with current CDC guidance and other State and Federal requirements. Nationally, the CDC has advised individuals should practice social distancing, avoid gatherings of more than10 individuals for high-risk populations and go into the community only for essential activities. https://www.cdc.gov/coronavirus/2019-ncov/community/large-events/mass-gatherings-ready-for-covid-19.html. Facilities should consider the high infection rates of COVID-19 and all geographic areas should be assumed to have high

levels of infected individuals unless proven differently based on adequate testing. States may have also imposed more restrictive limitations. The CDC guidance should not eliminate the opportunity for individuals to leave their homes. State and Federal agencies are issuing simultaneous guidance for COVID-19 and restrictive measures should be made in the context of competent, person-centered planning for each individual.

Can ICF/IID active treatment requirements be modified for COVID-19 cases?

Response: Under 42 CFR 483.440(c), a modification can be made to the client's Individual Program Plan (IPP) with the approval of the interdisciplinary team. Refer to your Emergency Preparedness (EP) policy and procedures to help address how to manage active treatment during an infection control emergency.

Can an ICF/IID utilize a day program building for quarantine, if necessary?

Response: We encourage ICF/IID programs to discuss these options with their state health agency and the State Survey Agency to address licensure issues, and to request any relevant models to the CMS 1135 waiver mailbox at 1135waiver@cms.hhs.gov and/or the appropriate CMS locations. This may also be addressed in the ICF/IID's emergency preparedness plan. We encourage active communication between the ICF/IID and day programs. There may be a number of alternate care models that ICF/IID programs could develop to separate positive COVID-19 patients from others. In all cases, ICF/IIDs should keep clear records of individuals who are moved, and should take appropriate measures to ensure the health and safety of those individuals during transit and at the new location.

How do we address the potential staffing shortage due to a 14-day quarantine for exposed health professionals who were not fully gowned and goggled which has the potential of wiping out our entire staffing [for one or more] [ICF/IID] homes?

Response: Please review the CDC website for updated information regarding exposure of Healthcare Professionals (HCPs). The CDC has provided recommendations on flexibility for asymptomatic, exposed HCPs to return to work "in selected circumstances". The CDC has established specific risk categories and provided recommendations regarding self-isolation and asymptomatic HCPs. https://www.cdc.gov/coronavirus/2019-ncov/hcp/guidance-risk-assesment-hcp.html. An ICF/IID facility may request a State specific 1135 waiver as a potential solution for staffing shortages. See the following link at https://www.cms.gov/files/document/covid19-emergency-declaration-health-care-providers-fact-sheet.pdf for the latest information for health care providers on 1135 waivers. For case-specific waivers, the facility administrator or designated representative should submit a request to 1135waiver@cms.hhs.gov. Facilities should follow their Emergency Preparedness program regarding emergency staffing. Additional information about CDC guidance regarding when health care workers may return to work can be found at https://www.cdc.gov/coronavirus/2019-ncov/healthcare-facilities/hcp-return-work.html.

When a client/resident has tested positive for COVID-19 and we implement quarantine procedures, client rights are immediately abridged and severe behaviors are likely to occur. This could be a situation where abuse via involuntary seclusion is an issue that has to be addressed. What is the guidance from CMS on balancing the CDC expectations with the rights of the individual?

Response: The health and safety of the clients/residents, visitors, and staff are the highest priority. For clients/residents that have been found positive for COVID-19 virus, the ICF/IID EP plan and Individual Program Plan (IPP) should include what specific procedures and steps should be taken for quarantine of the client while also taking every step reasonable to protect the rights, safety and health of the infected clients/residents and as well as those of the staff/s and other clients/residents. The facility quarantine procedures and steps should be consistent with the recommendations of the state and federal health agencies.

Facilities should adhere to the infection prevention and control practices issued by the CDC. It may be appropriate to consult with your state health agency for guidance based on the unique challenges of instituting infection prevention and control with individuals with intellectual disabilities in an ICF/IID. Currently, having clients/residents in their room with the door closed is the primary recommendation by the CDC for long-term care facilities (https://www.cdc.gov/coronavirus/2019-ncov/healthcare-facilities/prevent-spread-in-long-term-care-facilities.html). If that is not possible, options may include having the individual wear a facemask or other covering over their nose/mouth and provide whatever space restrictions are tolerated, such as six-foot social distancing. Facilities will have to consider multiple solutions to quarantine and preparedness is key in addition to good infection control practices.

We encourage facilities to work with all clients/residents to maintain good infection control practices and to perform thorough environmental cleaning. See the CDC link for cleaning recommendations at https://www.cdc.gov/coronavirus/2019-ncov/community/organizations/cleaning-disinfection.html. These steps may help clients/residents to better endure the stress and anxiety of confinement with less impact to their existing emotional and/or psychological disability. It will be important, to the degree possible, to allow these individuals to experience some of their daily routines, including access to outdoors, staff, and treatment while still under quarantine

How should facilities screen visitors and outside healthcare service providers?

Response: Facilities should actively screen and restrict visitation or healthcare service providers (e.g. contract therapist) by those who meet the following criteria:

1. Signs or symptoms of a respiratory infection, such as a fever, cough, or difficulty breathing.
2. Contact with someone with or under investigation for COVID-19 or ill with respiratory illness.
3. International travel within the last 14 days to countries with widespread or ongoing community spread. For updated information on countries visit: https://www.cdc.gov/coronavirus/2019-ncov/travelers/after-travel-precautions.html
4. Residence in a community where community-based spread of COVID-19 is occurring. For more information on mitigation plans for communities identified to be at risk, visit: https://www.cdc.gov/coronavirus/2019-ncov/community/index.html

For those individuals that do not meet the above criteria, facilities can allow entry but may require visitors or outside health care providers to use Personal Protective Equipment (PPE) such as facemasks as an extra precaution, as available. For those clients/residents that are not able to have visitors or outside healthcare providers visits due to having medical risk factors if they were to contract COVID-19 or for those who test positive for COVID-19, facilities should consider:
a) Offering alternative means of communication for people who would otherwise visit, such as virtual communications (phone, video-communication, etc.).

b) Creating/increasing listserv communication to update families or outside healthcare providers, such as advising to not visit.
c) Assigning staff as primary contact to families for inbound calls, and conduct regular outbound calls to keep families up to date.
d) Offering a phone line with a voice recording updated at set times (e.g., daily) with the facility's general operating status, such as when it is safe to resume visits.

When should ICF/IIDs or PRTFs consider transferring a client/resident with suspected or confirmed infection with COVID-19 to a hospital?

Response: ICF/IIDs or PRTFs with clients/residents suspected of or confirmed having COVID-19 infection should contact their state health agency for guidance. Clients/residents infected with COVID-19 may vary in severity from lack of symptoms to mild or severe symptoms or fatality. Initially, symptoms may be mild and not require transfer to a hospital as long as the facility can follow the infection prevention and control practices recommended by CDC. Facilities without an airborne infection isolation room (AIIR) are not required to transfer the client/resident assuming: 1) the client/resident does not require a higher level of care and 2) the facility can adhere to the rest of the infection prevention and control practices recommended for caring for a client/resident with COVID-19.

Facilities will want to take advantage of the telehealth benefits available to Medicare and Medicaid beneficiaries who will be able to receive various services through telehealth including common office visits, mental health counseling, and preventive health screenings. This will help ensure Medicare and Medicaid beneficiaries, who are at a higher risk for COVID-19, are able to visit with their doctor from their home, without having to go to a doctor's office or hospital which puts themselves or others at risk. Links for Medicare and Medicaid telehealth information: https://www.cms.gov/newsroom/fact-sheets/medicare-telemedicine-health-care-provider-fact-sheet and https://www.medicaid.gov/medicaid/benefits/telemedicine/index.html

Please check the following link regularly for critical updates, such as updates to CDC guidance for using PPE: https://www.cdc.gov/coronavirus/2019-ncov/infection-control/control-recommendations.html.

The client/resident may develop more severe symptoms and require transfer to a hospital for a higher level of care. Prior to transfer, emergency medical services and the receiving facility should be alerted to the client's/resident's diagnosis, and precautions to be taken including placing a facemask on the client/resident during transfer. If the client/resident does not require hospitalization, they can be discharged to home (in consultation with state public health authorities) if deemed medically, clinically and socially appropriate. Pending transfer or discharge, the facility should place a facemask on the client/resident and isolate him/her in a room with the door closed. If it is not possible for the client/resident to effectively wear a face mask, then a staff member with a face mask should provide supervision to ensure the client/resident stays isolated until transfer. For a client/resident that is being transferred, it will be important that staff communicate the appropriate amount of details and steps that will be followed in order to confirm the client/resident understands what to expect during the transfer. This would include providing any necessary devices, aids, and supports to help provide as much comfort and reassurance during the transfer experience.

When should an ICF/IID or a PRTF accept a client/resident who was diagnosed with COVID-

19 from a hospital?

Response: An ICF/IID or PRTF can accept a client/resident diagnosed with COVID-19 and still operate under transmission-based precautions for COVID-19 as long as the facility can follow CDC guidance for Transmission-based Precautions. If an ICF/IID or PRTF cannot follow the guidance, it must wait until these precautions are discontinued. CDC has released Interim Guidance for Discontinuing Transmission-Based Precautions or In-Home Isolation for Persons with Laboratory-confirmed COVID-19.

Information on the duration of infectivity is limited, and the CDC interim guidance has been developed with available information from similar coronaviruses. CDC states that decisions to discontinue transmission-based precautions in hospitals will be made on a case-by-case basis in consultation with clinicians, infection prevention and control specialists, and public health officials. Discontinuation will be based on multiple factors (see current CDC guidance for further details). https://www.cdc.gov/coronavirus/2019-ncov/infection-control/control-recommendations.html

Note: ICF/IIDs and PRTFs should admit any individuals that they would normally admit to their facility who are not symptomatic, including individuals from hospitals where a case of COVID-19 was/is present if they are able to adhere to the infection prevention and control practices recommended by the CDC.

Also, if possible, facilities should dedicate a wing or room/s for any clients/residents coming or returning from the hospital. This can serve as a step-down unit where they remain for 14 days with no symptoms.

Will ICF/IIDs or PRTFs be cited for not having the appropriate supplies?

Response: CMS is aware of that there is a scarcity of some supplies in certain areas of the country. State and Federal surveyors should not cite facilities for not having certain supplies (e.g., Personal Protective Equipment such as gowns, N95 respirators, surgical masks and alcohol-based hand rub (ABHR)) if they are having difficulty obtaining these supplies for reasons outside of their control. However, we do expect facilities to take actions to mitigate any resource shortages and show they are taking all appropriate steps to obtain the necessary supplies as soon as possible. For example, if there is a shortage of ABHR, we expect staff to practice effective hand washing with soap and water. Similarly, if there is a shortage of PPE (e.g., due to supplier(s) shortage which may be a regional or national issue), the facility should contact the state public health agency to notify them of the shortage, follow national guidelines for optimizing their supply: https://www.cdc.gov/coronavirus/2019-ncov/hcp/ppe-strategy/index.html, or identify the next best option to care for clients/residents. If a surveyor believes a facility should be cited for not having or providing the necessary supplies, the state agency should contact their CMS Location (previously termed Regional) Office.

Other considerations for facilities:

- Review CDC guidance for Infection Prevention and Control Recommendations for Patients with Confirmed COVID-19: https://www.cdc.gov/coronavirus/2019-ncov/infection-control/control- recommendations.html
- Increase the availability and accessibility of ABHRs, tissues, no touch receptacles for

disposal, and facemasks at healthcare facility entrances, waiting rooms, client/resident check-ins, etc., and reinforce strong hand-hygiene practices.
- Ensure ABHR is accessible in all client/resident-care areas including inside and outside client/resident rooms.
- Increase signage for vigilant infection prevention, such as hand hygiene and cough etiquette.
- Properly clean, disinfect and limit sharing of medical equipment between client/residents and areas of the facility.
- Provide additional work supplies to avoid sharing (e.g., pens, pads) and disinfect workplace areas (nurse's stations, phones, internal radios, etc.).

What other resources are available for facilities to help improve infection control and prevention?

Response: CMS urges providers to take advantage of several resources that are listed below:

CDC Resources:

- CDC Resources for Health Care Facilities: https://www.cdc.gov/coronavirus/2019-ncov/healthcare-facilities/index.html

- CDC COVID-19 symptoms and testing: https://www.cdc.gov/coronavirus/2019-ncov/symptoms-testing/index.html

- CDC disinfection control cleaning: https://www.cdc.gov/coronavirus/2019-ncov/community/organizations/cleaning-disinfection.html

- CDC Updates: https://www.cdc.gov/coronavirus/2019-ncov/whats-new-all.html

- CDC FAQ for COVID-19**:** https://www.cdc.gov/coronavirus/2019-ncov/infection-control/infection-prevention-control-faq.html

- CDC list of all state health agencies: https://www.cdc.gov/publichealthgateway/healthdirectories/healthdepartments.html

- Information on affected US locations*: https://www.cdc.gov/coronavirus/2019-ncov/cases-in-us.html*

CMS Resources:

- Medicaid Disaster Response Resources: https://www.medicaid.gov/state-resource-center/disaster-response-toolkit/federal-disaster-resources/index.html

- Medicaid telehealth benefits: https://www.medicaid.gov/medicaid/benefits/telemedicine/index.html

- CMS telemedicine for Medicare: https://www.cms.gov/newsroom/fact-sheets/medicare-telemedicine-health-care-provider-fact-sheet

- CMS ICF/IID Appendix J: https://www.cms.gov/Regulations-and-Guidance/Guidance/Manuals/downloads/som107ap_j_intermcare.pdf

- CMS PRTF Appendix N: https://www.cms.gov/Regulations-and-Guidance/Guidance/Manuals/downloads/som107ap_n_prtf.pdf

Advocacy Resources:

- https://selfadvocacyinfo.org/wp-content/uploads/2020/03/Plain-Language-Information-on-Coronavirus.pdf

- https://selfadvocacyinfo.org/wp-content/uploads/2020/03/Spanish-Plain-Language-Information-on-Coronavirus.pdf

Contact: Email QSOG_EmergencyPrep@cms.hhs.gov

NOTE: The situation regarding COVID-19 is still evolving worldwide and can change rapidly. Stakeholders should be prepared for guidance from CMS and other agencies (e.g., CDC) to change. Please monitor the relevant sources regularly for updates.

Effective Date: Immediately. This policy should be communicated with all survey and certification staff, their managers and the State/Regional Office training coordinators immediately.

/s/
David R. Wright

cc: Survey and Operations Group Management

EXHIBIT 5

Centers for Disease Control and Prevention
CDC 24/7: Saving Lives, Protecting People™

Coronavirus Disease 2019 (COVID-19)

People with Disabilities

Updated April 7, 2020

Print Page

COVID-19 is a new disease and we are still learning how it spreads, the severity of illness it causes, and to what extent it may spread in the United States.

Disability alone may not be related to higher risk for getting COVID-19 or having severe illness. Most people with disabilities are not inherently at higher risk for becoming infected with or having severe illness from COVID-19. However, some people with disabilities might be at a higher risk of infection or severe illness because of their underlying medical conditions. All people seem to be at higher risk of severe illness from COVID-19 if they have serious underlying chronic medical conditions like chronic lung disease, a serious heart condition, or a weakened immune system. Adults with disabilities are three times more likely than adults without disabilities to have heart disease, stroke, diabetes, or cancer than adults without disabilities.

You should talk with your healthcare provider if you have a question about your health or how your health condition is being managed.

Disability groups and risk

If you have one of the disability types listed below, you might be at increased risk of becoming infected or having unrecognized illness. You should discuss your risk of illness with your healthcare provider.

- People who have limited mobility or who cannot avoid coming into close contact with others who may be infected, such as direct support providers and family members
- People who have trouble understanding information or practicing preventive measures, such as hand washing and social distancing
- People who may not be able to communicate symptoms of illness

Protect yourself

If you or someone you care for are at higher risk of getting very sick from COVID-19, take steps to prevent getting sick. In addition to practicing everyday preventive actions, people with disabilities who have direct support providers can help protect themselves from respiratory illness in the following ways:

- Ask your direct support provider if they are experiencing any symptoms of COVID-19 or if they have been in contact with someone who has COVID-19
- Tell your direct service provider to
  - Wash their hands when they enter your home and before and after touching you (e.g., dressing, bathing/showering, transferring, toileting, feeding), handling tissues, or when changing linens or doing laundry. Learn more about proper handwashing.

- Clean and disinfect frequently touched objects and surfaces (e.g., counters, tabletops, doorknobs, bathroom fixtures, toilets, phones, keyboards, tablets, bedside tables), and equipment such as wheelchairs, scooters, walkers, canes, oxygen tanks and tubing, communication boards and other assistive devices. Refer to CDC's General Recommendations for Routine Cleaning and Disinfections of Households.

Prepare

There are some additional things people with disabilities can do to prepare during the COVID-19 outbreak:

- Plan what you will do if you or your direct support provider gets sick. Create a contact list of family, friends, neighbors and local service agencies that can provide support in case you or your direct support provider becomes ill or unavailable.
- Plan at least two ways of communicating from home and work that can be used rapidly in an emergency (e.g., landline phone, cell phone, text-messaging, email). Write down this information and keep it with you.
- Have enough household items and groceries so that you will be comfortable staying home for a few weeks, at least a 30-day supply of over the counter and prescription medicines and any medical equipment or supplies that you might need. Some health plans allow for a 90-day refill on prescription medications. Consider discussing this option with your healthcare provider. Make a photocopy of prescriptions, as this may help in obtaining medications in an emergency situation.

About COVID-19

- Coronavirus disease is a respiratory illness that can spread from person to person. The virus is thought to spread mainly between people who are in close contact with one another (within about 6 feet) through respiratory droplets produced when an infected person coughs or sneezes. It is also possible that a person can get COVID-19 by touching a surface or object that has the virus on it and then touching their own mouth, nose, or eyes. For more information go to CDC's Fact Sheet- What you need to know about coronavirus disease 2019 (COVID-19) .
- Risk of infection with COVID-19 is higher for people who are in close contact with someone known to have COVID-19, such as healthcare workers, direct support providers, and household members. Other people at higher risk for infection are those who live or have recently been in an area with ongoing spread of COVID-19.

Prevention and treatment

There is currently no vaccine to protect against COVID-19. The best way to prevent infection is to take everyday preventive actions, like avoiding close contact with people who are sick and washing your hands often. There is no specific antiviral treatment for COVID-19. People with COVID-19 can seek medical care to help relieve symptoms.

More Information

People Who Need to Take Extra Precautions
People Who Are at Higher Risk for Severe Illness
Other At-Risk Populations
Direct Service Providers for People with Disabilities
Symptoms & Testing
If You Are Sick or Caring for Someone
Cases and Updates

Page last reviewed: April 7, 2020
Content source: National Center for Immunization and Respiratory Diseases (NCIRD), Division of Viral Diseases

EXHIBIT 6

COVID-19 Can Have Serious Effects on People with Mental Health Disorders

Share on Pinterest
Experts say people with severe mental illness are more likely to contract the new coronavirus and are less likely to get proper treatment for its disease, COVID-19. Getty Images

- **Experts say people with severe mental illness face serious issues during the COVID-19 pandemic.**
- **They say people with mental illness have lifestyles that increase their risk for contracting the new coronavirus.**
- **They also have more underlying health conditions that raise their risk for developing more serious cases of COVID-19 if they contract the virus.**
- **In addition, mental health facilities could face additional strain as more of their clients are diagnosed with COVID-19.**

All data and statistics are based on publicly available data at the time of publication. Some information may be out of date. Visit our coronavirus hub and follow our live updates page for the most recent information on the COVID-19 outbreak.

So far, older adults, along with those who have underlying health conditions, have been hit the hardest by the COVID-19 outbreak, with many developing severe, life threatening illnesses.

Another group that's expected to be acutely affected by the pandemic include those who have severe mental illness.

A new paperTrusted Source published in JAMA Psychiatry says a crisis is headed for the country's mental healthcare system as state psychiatric hospitals and local clinics gear up for an influx of people with COVID-19.

Mental health issues often coincide with a unique set of challenges that make it difficult for people to access even the most basic necessities, such as food, medications, stable housing, and healthcare.

Combined, all of these factors put people with severe mental illness at a much higher risk for contracting and transmitting the new coronavirus and dealing with COVID-19.

The challenges

Dr. Fumi Mitsuishi, director of the UCSF/ZSFG Division of Citywide Case Management in San Francisco, says there's a long list of challenges that put people living with psychiatric disorders — such as schizophrenia, bipolar disorder, or depression — at a higher risk from severe COVID-19.

"We're talking about a population that struggles with being housed, being able to feed themselves, being able to take care of medical issues, having enough of an income," Mitsuishi told Healthline.

Many of the people Mitsuishi sees at Citywide Case Management struggle with holding down a job. Some take home just $25 a week after paying rent.

Oftentimes, they're temporarily housed in congregate living situations, such as a shelter or center designed to get them into more permanent housing.

It's close living quarters. People sleep alongside one another and share a bathroom.

Access and underlying conditions

If one person comes down with COVID-19, there's a good chance the virus will rip through the congregated community.

Those with severe mental illness oftentimes don't have a smartphone, nor do they have laptops or access to TV, so they must rely on mental health clinicians to get the latest updates about the pandemic, according to Dr. Collin Reiff, an addiction psychiatrist at NYU Langone Health.

This also means that in a time when many mental health professionals and clinicians have started consulting with their clients remotely, those who don't have a device don't get the care they need.

“How do they suddenly make their appointments? They don’t,” Reiff said.

Layered on top of that, substance misuse is prominent among people with mental illness, Reiff told Healthline.

Substance misuse is linked to an increased susceptibilityTrusted Source to infectious diseases. It may also make people more prone to risky behavior.

Reiff says it may therefore prevent people from taking the proper safety, self-care, and social distancing measures.

The rates of smoking among those with mental illness are higher — about 60 to 70 percentTrusted Source of people with schizophrenia regularly smoke cigarettes, says Mitsuishi.

That increases their risk for asthma, chronic obstructive pulmonary disease (COPD), and other respiratory illnesses that make someone more likely to experience COVID-19 complications.

Diabetes, hypertension, heart diseaseTrusted Source, poor cholesterol — all key risk factors for serious COVID-19 complications — are also common in this population.

“Their biological age is much higher than their actual age. Our clients are in very high-risk categories for most complications from most illnesses, and COVID is one of them,” Dr. Carrie Cunningham, the medical director of Citywide Case Management, told Healthline.

Pneumonia and influenza are some of the leading causes of death in people with mental illness, largely due to underlying lung disease, Cunningham adds.

Distrust of medical community

Many people with severe mental illness also have a strong distrust for the healthcare system from previous traumatic experiences cycling in and out of hospitals.

According to Cunningham, it’s common for people with severe mental illnesses to refuse to go to the hospital.

Because of this, they put off seeking treatment even if they have symptoms. And when it comes to COVID-19, a delay in treatment can be a matter of life or death.

Then there’s the stigma of getting a respiratory disease like COVID-19. That stigma — which may manifest as a deep shame or embarrassment for getting sick — only weighs on the already heavy stigma people can carry from mental illness, which can make it even more difficult for them to lift out of their living situation.

“It’s really the stigma that leads to folks who have mental illness being shut away from opportunities. Employment is one of them, being trusted by family members, and being therefore protected and helped,” Mitsuishi said.

Strain on the system

Psychiatric units will have to rapidly adapt to the ever-changing state of the pandemic.

Among other things, nonessential activities and group therapy sessions have been postponed.

“You’re going to take medication to be stabilized, and that’s pretty much it. There are parts of the equation missing,” Reiff said.

At Citywide Case Management, Mitsuishi and Cunningham’s team has been hustling to nail down the best quarantine, screening, and caregiving procedures.

Besides the cancellation of group therapy sessions, hot meals and medications are being distributed at the front door only.

Right now, the staff has enough personal protective equipment (PPE) and is giving out about 100 meals at the front door every day. They provide about 7,000 meals a week to nearby facilities that are housing people with mental illness.

But there’s a growing fear that there will soon be shortages — of not just PPE but food and medications too.

The workers are also concerned about a bed shortage at psychiatric hospitals, where the number of beds is already limited due to their high cost.

There aren’t designated COVID-19 floors at state psychiatric hospitals, and given the open layout, where beds sit next to one another, there’s an opportunity for the virus to spread readily between patients.

“If you have an infection happening in the unit, it’s going to spread super rapidly,” Mitsuishi said. “If we start to lose units at state hospitals [to COVID-19], then it’s going to be really scary.”

ReportsTrusted Source have shown that respiratory infections, including the flu, account for the most outbreaks in psychiatric units.

COVID-19, which is thought to be more contagious than influenza, could strike these places just as hard.

Preparing and gathering resources takes time. Psychiatric units and mental health clinics need to act quickly to ensure they have a plan in place when an outbreak strikes.

“It’s all about timing, right,” Mitsuishi said. “We are flattening the curve so we can prepare for as long as possible of a surge [due to the coronavirus].”

EXHIBIT 7

VIEWPOINT

Addressing the COVID-19 Pandemic in Populations With Serious Mental Illness

Benjamin G. Druss, MD, MPH
Rollins School of Public Health, Emory University, Atlanta, Georgia.

The coronavirus disease 2019 (COVID-19) pandemic will present an unprecedented stressor to patients and health care systems across the globe. Because there is currently no vaccine or treatment for the underlying infection, current health efforts are focused on providing prevention and screening, maintaining continuity of treatment for other chronic conditions, and ensuring access to appropriately intensive services for those with the most severe symptoms.[1]

Disasters disproportionately affect poor and vulnerable populations, and patients with serious mental illness may be among the hardest hit. High rates of smoking in this population may raise the risk of infection and confer a worse prognosis among those who develop the illness.[2] Residential instability and homelessness can raise the risk of infection and make it harder to identify, follow up, and treat those who are infected.[3] Individuals with serious mental illnesses who are employed may have challenges taking time off from work and may lack sufficient insurance coverage to cover testing or treatment. Small social networks may limit opportunities to obtain support from friends and family members should individuals with serious mental illness become ill. Taken together, these factors may lead to elevated infection rates and worse prognoses in this population.

What strategies are available to mitigate the outcome of this epidemic among patients with serious mental illness? Federal preparedness policies developed in the wake of complex disasters have increasingly embraced the notion of whole community preparedness, which supports building and supporting structures at multiple levels to prepare and respond, particularly for vulnerable populations.[4] Within the public mental health care system, this includes engagement with mental health service users, clinicians, and federal and state policies.

Supporting Patients With Serious Mental Illness

People with serious mental illnesses should be provided with up-to-date, accurate information about strategies for mitigating risk and knowing when to seek medical treatment for COVID-19. Patient-facing materials developed for general populations will need to be tailored to address limited health literacy and challenges in implementing physical distancing recommendations because of poverty and unstable living situations. Messaging will need to provide assurances that those who seek care will not face penalties with regards to cost or immigration status. Patients will need support in maintaining healthy habits, including diet and physical activity, as well as self-management of chronic mental and physical health conditions.

It will also be important to address the psychological and social dimensions of this epidemic for patients. Worry could both exacerbate and be exacerbated by existing anxiety and depressive symptoms. Physical distancing strategies critical for mitigating the spread of disease may also increase the risk of loneliness and isolation in this population. Those who become ill may face dual stigma associated with their infections and their mental health conditions. For any given patient, psychological symptoms will emerge in a unique personal and social context that should be considered in developing a treatment plan.

Empowering Mental Health Clinicians

Mental health clinicians are often the primary point of contact with the broader health care system for their patients with serious mental illnesses, and as such will represent the first responders to the COVID-19 pandemic for many of these individuals. Mental health clinicians need training to recognize the signs and symptoms of this illness and develop knowledge about basic strategies to mitigate the spread of disease for both in their patients and themselves. Clinicians should have discussions with their patients about how best to implement the strategies.

Clinicians will need support in maintaining their own safety and well-being. Where possible, services should be delivered via telehealth rather than in person, and when in-person visits are necessary, in individual rather than group formats. Child and elder care should be made available for mental health clinicians working extra shifts. Support from colleagues will be essential for maintaining physical, mental, and social well-being, particularly if the pandemic is of an extended duration.

Strengthening Mental Health Care Systems

The COVID-19 pandemic is likely to place a major strain on community mental health centers and state psychiatric hospitals. These facilities have limited capacity to screen for or treat medical conditions, and few have existing relationships with local or state public health agencies. It is critical for these organizations to develop continuity-of-operations plans to ensure that they can maintain vital functions in the face of staff illnesses or shortages of psychotropic medications. Clinics will need protocols for identifying and referring patients at risk for infection and self-quarantine strategies for clinicians who develop symptoms of the illness. Adequate environmental protections including well-ventilated spaces, easy access to handwashing, and personal protective equipment should be available. Institutional settings, including state psychiatric hospitals, nursing homes, and long-term care facilities, will be at particularly high risk for

Corresponding Author: Benjamin G. Druss, MD, MPH, Rollins School of Public Health, Emory University, 1518 Clifton Rd, Atlanta, GA 30322 (bdruss@emory.edu).

outbreaks and need to ensure that they have contingency plans to detect and contain them if they occur.

Expanding Mental Health Policies

The coming weeks will see a wave of new federal legislation and regulations and state policies developed to mitigate the health and economic outcomes of the COVID-19 outbreak.[5] These policies will have particular urgency for populations with serious mental illness because of their elevated risks. State mental health authorities will play a critical role in creating and administering policies regarding COVID-19 in their state hospitals and community mental health clinics. The role of social policies, such as the Supplemental Nutrition Assistance Program, housing support, and paid sick leave for hourly employees will be vital for ensuring the health and well-being of this population.

The COVID-19 pandemic will create unprecedented health and social challenges both in the US and internationally. People with serious mental illnesses will be at uniquely high risk during this period, as will be the public mental health care system central to delivering their care. Careful planning and execution at multiple levels will be essential for minimizing the adverse outcomes of this pandemic for this vulnerable population.

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EXHIBIT 8

urgently needed. China's endeavours to foster medical humanities education reforms should be actively promoted at the level of research, policy, and practice.

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*Angela P Fan, Russell O Kosik, Selina S Lien, Yunung Hsu, Lihong Fan, Dan Li, Lei Huang, Xudong Zhao, Yuanpeng Ren, Baisheng Jiang, Qi Chen,
fan_angela@hotmail.com

School of Medicine, National Yang-Ming University, Taipei, Taiwan (APF, SSL, YH); 10th People's Hospital, Tongji University School of Medicine, Shanghai, China (ROK, LF, DL); Tongi Hospital, Tongji University School of Medicine, Shanghai, China (LH); Tongji University School of Medicine, Shanghai, China (XZ); and Nanjing Medical University, Nanjing, China (YR, BJ, QC)

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COVID-19 testing and patients in mental health facilities


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People residing in psychiatric treatment facilities are at high risk for coronavirus disease 2019 (COVID-19). Given the absence of a vaccine or treatment, prevention is the primary guard against adverse events, such as acute respiratory distress syndrome and death. However, prevention requires keeping infected and uninfected patients apart as much as possible.

Because some patients with COVID-19 can be contagious yet asymptomatic, especially in the initial days after infection, knowing who is infected requires timely diagnostic testing as well as when and how a patient was exposed and when symptoms began. This could be challenging in individuals with psychiatric or substance use disorders as some are unable to recall or are unaware of potential exposures and symptom onset.

Even under optimal conditions, current diagnostic tests do not effectively identify infected individuals and, as more people become infected, the number of false negatives increases. Furthermore, new polymerase chain reaction and serological tests arise each week, often with limited performance information, which adds to the confusion about COVID-19 tests.[1]

People with psychiatric conditions or substance use disorders, particularly those in residential treatment or inpatient facilities, are at increased risk of exposure to COVID-19, not only because of the difficulty in evaluating their medical symptoms and history, but also because of frequent patient turnover, limited space and staff, and general resource constraints in many facilities. Patients infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)—the virus responsible for the development of COVID-19—pose a substantial threat of spreading the virus because they come in contact with other susceptible individuals given the close quarters and communal living environments. Furthermore, these patients are at higher risk for complications of COVID-19 because they frequently have underlying medical conditions that worsen their prognosis (eg, cardiac disease, history of smoking).

The vulnerability of institutionalised populations has been noted by clinicians and researchers, and we extend this work by drawing attention to this particularly high-risk subgroup and the problems posed by the performance of current diagnostic technology.[2,3]

One solution would be to test all individuals for COVID-19 before entry into treatment facilities. Testing capacity has improved; however, access remains limited and test sensitivity is modest, which results in false negatives.[4,5] Test performance is further compromised by variations in test quality, sample collection, and duration of symptom onset, increasing the potential for error.[6] For example, for a patient presenting with disorganised thinking or altered mental status, determining the date of onset of non-specific symptoms such as a cough might be difficult. Thus, the pretest probability of infection with SARS-CoV-2 could be

hard to estimate. Fundamentally, when the sensitivity of a test is limited and the disease course for a patient is unknown, the test outcome could be unreliable and infectious patients could be placed erroneously in treatment facilities.

Already, there has been evidence of rapid spread of COVID-19 through long-term care facilities and inpatient psychiatry units,[7,8] with several reporting patient deaths attributed to COVID-19. Non-pharmacological interventions such as physical distancing and frequent handwashing can be difficult to implement in these types of inpatient or residential settings, as some individuals might not be able to adhere to recommendations.

Best practice should involve screening all patients for symptoms of COVID-19, particularly before admission, and a protocol should be implemented for management of inpatients who develop symptoms.[9]

One potential strategy for improving detection could involve testing all patients for COVID-19 at two or more time points before entry to the inpatient unit to mitigate the risk of false negative results for those with uncertain time of disease onset. Another would be to require sample testing from multiple body sites with more than one sample, analogous to blood culture protocols, which could address concerns about sampling technique. Patients infected with SARS-CoV-2 should remain separated from other people until testing indicates they are no longer infectious.

As serological tests and additional diagnostic or risk information become available, diagnostic certainty and detection should improve, at which point existing protocols should be adapted. Because of the potential for rapid spread and serious complications, implementation of such preventative efforts must occur immediately. This should be done in combination with the development of a rigorous evidence base monitoring diagnostic testing and disease transmission in this rapidly changing environment by use of creative study designs.

In addition to testing patients, prevention should centre around providing safe conditions for patients and staff. The United States Centers for Medicare and Medicaid Services recently released guidelines allowing for patient separation on the basis of COVID-19 status for patients in long-term care facilities.[10] Analogous considerations for individuals with mental illness in residential or acute care facilities would probably benefit this population.

These recommendations are burdensome, but necessary given increasing reports of rapid spread within facilities housing susceptible individuals. The structure of these facilities and patient populations make monitoring illness course and preventing the spread of COVID-19 more difficult, but these risks can be mitigated by employing testing strategies that attempt to lift the shroud of false negative test results.

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*Nicole M Benson, Dost Öngür, John Hsu
nbenson@mgh.harvard.edu

McLean Hospital, Harvard Medical School, Belmont, MA 02478, USA (NMB, DÖ); Department of Psychiatry (NMB), and Mongan Institute (JH), Massachusetts General Hospital, Boston, MA, USA; and Department of Health Care Policy, Harvard Medical School, Boston, MA, USA (JH)

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EXHIBIT 9

Psychosocial Interventions to Reduce Premature Mortality in Patients With Serious Mental Illness

The mortality rate is unacceptably high in patient with serious mental illnesses. Several psychosocial interventions have been developed that may benefit these patients.

TABLE. Factors associated with the higher mortality rates in patients with severe mental disorders[16]

• Factors related to the disorder itself (due to decline in cognitive functioning, and tendency to avoid routine check-up visits and neglect of physical health)
• Factors related to pharmacological treatments (eg, metabolic adverse effects of antipsychotic medications)
• Factors related to the organization of mental health system and attitudes of health professionals (due to lack of parity between physical and mental health services)
• Factors related to patients' unhealthy lifestyle behaviors (ie, inactivity, poor diet, use of psychoactive substances, altered circadian rhythms, smoking)

SPECIAL REPORT: ADDRESSING MORTALITY

Compared with the general population, patients with serious mental illness (SMI), ie, schizophrenia, major depression, and bipolar disorders, have higher levels of morbidity, poorer health outcomes, and higher mortality rates.[1] In particular, life expectancy is reduced up to 25 years.[2] The causes of this premature mortality have been extensively analyzed, and the vast majority is due to the higher incidence of physical health problems, such as cancer as well as cardiovascular, respiratory, metabolic, and infectious diseases.[3,4] The higher mortality rates are due to different factors, which are summarized in the **Table**.

This mortality gap between the general population and people with SMI is considered a "public health scandal."[5] Hence, several international organizations have advocated for individual and community-based interventions to reduce mortality in these patients. In particular, the World Health Organization has recently developed international guidelines on how to improve physical health in people with severe psychiatric disorders and has provided a set of actions to be undertaken by national health systems, including

control of risk factors, scaling up management in primary health care, and development of national policies.[6] According to WHO, since the premature mortality is a complex phenomenon resulting by the interaction of several protective and risk factors, a single approach is likely to be inadequate. A multilevel approach would be more appropriate for the long-term management of physical and mental health conditions.

The role of psychosocial interventions for improving lifestyle behaviors

Several psychosocial interventions, including behavioral, educational, and psychological components, have been developed worldwide in order to improve lifestyle behaviors in patients with SMIs.[7] These approaches, if proved to be effective, would have to be disseminated on a large scale.

Recently developed in Denmark, CHANGE is an intervention that targets physical inactivity, unhealthy dietary habits, and smoking, and is facilitates contact to the general practitioner.[8] It is based on the theory of stage of change, motivational interviewing, and an assertive approach adapted from the assertive community treatment. The three methods were incorporated in four manuals with detailed descriptions of the intervention addressing care-coordination, smoking cessation, healthy diet, and increased physical activity. The intervention is led by a coach, who supports the patient in setting up individual goals and paying attention to his or her priorities, values, and life conditions. The coaches are available for short message services, phone calls, or home visits, as needed. They are health professionals (eg, occupational therapists, physiotherapists, dieticians) with clinical training in psychiatry. Findings from the CHANGE trial indicate that intervention was effective in reducing the mean age-standardized 10-year cardiovascular risk.[8,9]

In the US, Green and colleagues,[10] have developed the STRIDE intervention, which is a 12-month intervention consisting of three phases:
1. An intensive phase of weekly group sessions for 6 months covering information on nutrition, physical activity, and lifestyle changes
2. A maintenance intervention phase, covering the same areas of previous phase through problem solving and motivational enhancement
3. Individual monthly contacts for the remaining 6 months of the intervention
Using a manualized protocol, participants are asked to implement a series of specific strategies for achieving changes in behavior, activity level, and weight. In particular, participants are encouraged to routinely monitor food intake, calories, and physical activity, to set reasonable short-term goals, to formulate specific plans, and to develop social support. Manuals are available for download and can be easily used in clinical care. Patients who received the STRIDE intervention reported significant weight reduction.

The SHAPE program was developed for obese people with SMIs.[11] The intervention includes gym membership, weekly individual meetings with a certified fitness trainer, and information on healthy eating. A motivational component is also included in the program, coupled with a specific focus on the management of psychiatric symptoms that can interfere with exercise and healthy eating. A significant BMI reduction was seen in the patients who took part in the program.

MOVE! is a weight management program developed by the Veterans Health Administration, which has been manualized in order to address the needs of veterans with serious mental illness.[12] MOVE! is a 6-month weight management approach that includes psychoeducation as well as behavioral and motivational strategies that focus on nutritional counselling, caloric expenditure, and portion control. During the sessions, visual aids are used. Although results from MOVE! participants did not differ from those of the control group, this program has been adapted to be provided through 30 Internet-based interactive educational modules (WebMOVE).[13] Compared with patients who received the in-person intervention, those who received the WebMOVE intervention reported a more significant weight loss-highlighting the possible role of the Internet for these programs.

We have recently developed the LYFESTYLE intervention, a new psychosocial approach that aims to improve physical health in people with SMI.[14] It is a 5-month group intervention that includes elements taken from psychoeducation, cognitive-behavioral therapy, and motivational interview. At each session, participants are provided with booklets, homework, and daily diaries to keep track of any changes. The sessions end with a 20-minute moderate physical activity. The primary outcome is a reduction of BMI and an improvement on the Framingham and HOMA indexes at the end of the intervention. At 2 years of follow up, these outcome measures are expected to increase and can be considered as an indirect measure of mortality preventionThe multicentric randomized controlled trial that compared the LIFESTYLE intervention with a control informative intervention included 402 patients.

A collection of the most promising psychosocial interventions to improve lifestyle behaviors in people with SMIs was recently published.[15] All available psychosocial interventions differ in the target population (individuals or groups; diagnostically closed or open

to different categories of patients); the inclusion of different psychosocial components in the intervention (eg, motivational, educational, problem-solving, self-help); the type of health professionals involved (eg, psychiatrists, psychologists, nurses, dieticians, personal trainers); the duration of the intervention and the provision of booster sessions.

It is not clear which format yields the best results. In fact, while the individual format prioritizes the motivational component and allows treatment personalization based on the needs of each participant, the group format allows patients to share their experiences and to provide reciprocal support.

Another important consideration is the involvement of a multidisciplinary team. When the intervention is provided by mental health professionals only, its long-term efficacy is low. It is likely that specific components of the interventions (ie, those related to physical activities or diet habits) can be more easily changed by involving professionals with specific knowledge and training. Of course, the cost-to-benefit ratio should always be considered, in particular the costs related to the recruitment of professionals different from those already working in mental health.

Many trials have included a motivational component, which represents the core active ingredient for most psychosocial interventions that aim to improve lifestyle behaviors in patients with SMI. The target of the different proposed approaches varies significantly; in some cases, interventions are focused on diet and healthy food, while in other cases different aspects of lifestyle behaviors (such as smoking, regular physical activity, sleep hygiene) are prioritized. Moreover, the duration of the intervention is very heterogeneous. Some interventions last 3 months, while others can last up to 2 years. With longer interventions, the most relevant difficulties are related to the high rate of patient drop-outs and the excessive workload for clinicians who are involved in the intervention. However, the “minimum effective dosage” is not yet clear.

Conclusions

Psychosocial interventions that target lifestyle behaviors represent a promising approach for challenging the premature mortality in patients with SMI. However, their use in clinical practice is rare and preventive strategies that can be easily integrated in routine care should be adopted. In particular, clinicians should regularly check lifestyle behaviors of their patients and provide them with adequate information on the positive effects of healthy diet, physical activity, and smoking cessation. Specific training on these aspects should be included in educational curricula for residents and trainees, with a particular focus on motivational interviewing, psychoeducation, and problem-solving. An ideal approach should not be too long and should be conducted by trained mental health clinicians in conjunction with other health professionals. The group format seems to be the best option, as it reduces the costs and increases patients’ motivation. There is still a long way to go, but at least now the way is tracked.

Disclosures:

Dr Fiorillo *is Full Professor, and* **Dr Sampogna** *and* **Dr Luciano** *are Assistant Professors, Department of Psychiatry, University of Campania “L. Vanvitelli,” Naples, Italy.* *The authors report no conflicts of interest concerning the subject matter of this article.*

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EXHIBIT 10

The Coronavirus Crisis

COVID-19 Infections And Deaths Are Higher Among Those With Intellectual Disabilities

June 9, 2020 · 5:00 AM ET
Heard on Morning Edition

JOSEPH SHAPIRO

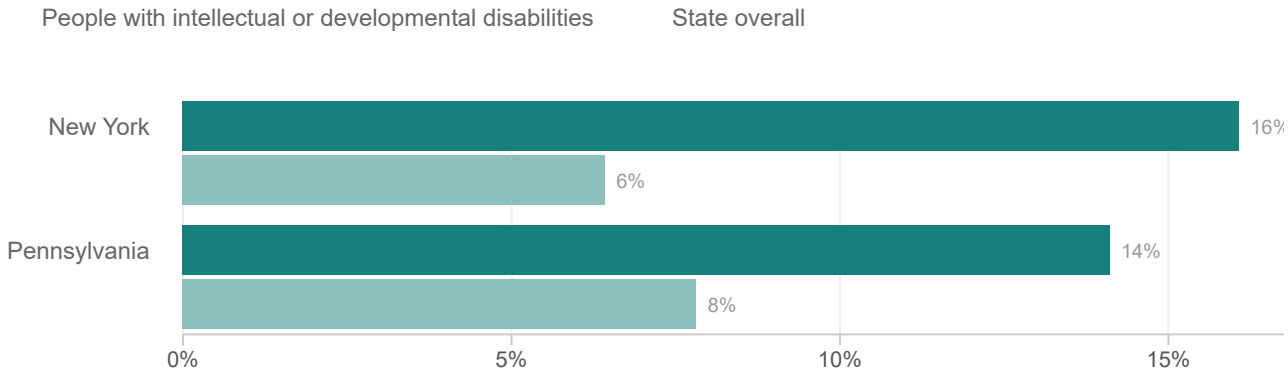
4-Minute Listen

PLAYLIST Download

Transcript

People With Intellectual Disabilities And Autism Die Of COVID-19 At A Higher Rate

In New York and Pennsylvania, COVID-19 case-fatality rates for people with intellectual and developmental disabilities are higher than the states' overall rates. (Case-fatality rates are deaths as a percentage of total confirmed cases within the population.)



Notes

Data as of June 3. Numbers for people with intellectual disabilities reflect those who get services from the state.

Source: New York State Department of Health, Pennsylvania Department of Health, Pennsylvania Office for People with Developmental Disabilities, New York Office for People with Developmental Disabilities

Credit: Stephanie Adeline/NPR

People with intellectual disabilities and autism who contract COVID-19 die at higher rates than the rest of the population, according to an analysis by NPR of numbers obtained from two states that collect data. They also contract the virus at a higher rate, according to research looking into group homes across the United States.

In Pennsylvania, numbers obtained by NPR show that people with intellectual disabilities and autism who test positive for COVID-19 die at a rate about twice as high as other Pennsylvania residents who contract the illness.

In New York, the state with the most deaths from COVID-19, people with developmental disabilities die at a rate 2.5 times the rate of others who contract the virus.

The numbers in Pennsylvania are compiled by the Office of Developmental Programs of the Pennsylvania Department of Human Services and count people who get state services while living in group homes, state institutions or in their own homes. As of June 2, there were 801 confirmed cases and 113 deaths among people with intellectual disabilities and autism. In New York, NPR calculated data obtained from the New York State Office for People with Developmental Disabilities. Of people who get state services from that office, 2,289 have tested positive for COVID-19 and 368 have died.

The high rate of death "is disturbing, but it's not surprising," says Scott Landes, an associate professor of sociology at Syracuse University's Maxwell School of Citizenship and Public Affairs.

He's been collecting his own data from state and private research groups and says people with developmental disabilities who live in group homes have some of the highest death rates from COVID-19 in the country.

"They're more likely — four times more likely, we're showing — to actually contract COVID-19 than the general population," he says. "And then if they do contract COVID-19, what we're seeing is they're about two times more likely to die from it."

That's higher than the death rates for Hispanics and African Americans.

Landes co-authored a recent study that used private health records to show that 18- to 74-year-olds with developmental disabilities, mostly those diagnosed with autism, who contracted COVID-19 died at nearly twice the rate as others.

THE CORONAVIRUS CRISIS

Hospital Visitor Bans Under Scrutiny After Disability Groups Raise Concerns Over Care

THE CORONAVIRUS CRISIS

In New York Nursing Homes, Death Comes To Facilities With More People Of Color

Landes says there are two reasons for the high death rates. People with developmental disabilities are far more likely to have a preexisting health condition, such as respiratory disease, that adds to their risk. They're much more likely, than even elderly people, to live in a setting with roommates and staff like group homes where two or four or 10 or more people live together. About 13% to 20% of people with developmental disabilities live in such settings, Landes notes, compared with only about 6% of people over age 65.

"You reside with multiple roommates, with staff coming in and out," says Landes, "your chances of actually contracting COVID are high. And then if someone in your home gets it, it's like there's nowhere you can go."

There has been a lot of attention to the deaths in nursing homes, and with good reason. About a third of all deaths nationwide from COVID-19 have been linked to them. According to the federal Centers for Medicare & Medicaid Services, there have been at least 31,782 deaths of nursing home residents from COVID-19 as of May 31. The CMS total does not count nursing home staff who died.

Medics suit up in personal protective equipment as they prepare to pick up a patient in severe respiratory distress from a group home in the Borough Park neighborhood of Brooklyn on May 11.

Spencer Platt/Getty Images

Still, says Nicole Jorwic, senior director for public policy at the Arc, a group that represents people with intellectual and developmental disabilities, there are consequences to paying less attention to people who live in other care home settings.

One result, she says, is that it has been harder for the groups that serve people with disabilities to get personal protective equipment or extra pay for staff workers. In most states, these workers don't get the bonus pay that is sometimes offered to other front-line health care workers and, in some states, the staff who serve people in group homes or their own homes aren't considered essential workers.

"You don't go into a hospital and some doctors have on masks and some don't. Or some are underpaid and some are not," says Antonio McCall, a direct service provider who works with two men at a Philadelphia group home. "No, everyone gets what they're working for. Everyone's covered with protection, because that's what's required."

There have been no infections at the house where McCall works, but there have been some outbreaks of COVID-19 — and even a death — at others. He says his agency managed to find masks for him, and he has received some extra pay.

And McCall is careful. He doesn't want to bring an infection into the group home or his own home, where he helps care for his mother, who has an underlying health condition, and is raising his niece and nephew.

In New York, a direct service professional working in a group home makes little money — "at or below the poverty line," in the mid $20,000s a year, says Tom McAlvanah, president of New York Disability Advocates, a coalition of service providers. He says it has been hard to keep workers healthy and on the job. They're vulnerable not only because of where they work, but because they often rely on public transportation.

McAlvanah says New York's Medicaid program, the main source of payment for group home providers, has failed to increase reimbursements even before the coronavirus pandemic. Now, he says, group home residents have stopped going to work and group home providers have had to pay staff — without government reimbursement — to work more hours and overtime to run the group homes where residents now spend their full days.

That's the case in most states, although Colorado and several others did increase Medicaid resources to providers. The CARES Act, the coronavirus relief act signed into law in March, became a source of extra funding, but only through the end of June.

Provider agencies say that, on average, they've spent a third of their annual revenue on unexpected costs from the pandemic and have cash reserves to cover a month or less of operations, according to a recent national survey by the American Network of Community Options and Resources, a trade association for groups that provide services to people with disabilities.

"For years and years and years, people we serve in group homes like this, they're the forgotten people," says Todd Goodwin, who runs John F. Murphy Homes, a large provider agency in Maine. "Nobody sees them. Nobody notices them. We see that repeatedly through policy, we see that in financing at the state and federal level. It's been an issue for years."

In Washington state, there was a Zoom meeting last month of men and women with developmental disabilities who belong to an advocacy group called People First of Washington. They spoke of their opposition to state budget cuts that, they worried, would cut off public transportation that they depend on to get to work or cut the hours of their state-funded caregivers. And they were worried about the effects of the coronavirus.

Shane Cody Fairweather, who lives in his own apartment in Chewelah, Wash., with support from service providers, said in an interview that he worries that people like him are not getting attention, despite their risks for contracting COVID-19.

"We're part of society. We're more vulnerable," he says. "It should be on equal footing. They should be paying attention to the elderly and the disabled as well."

Fairweather says there have been no outbreaks of the coronavirus in the apartments where he lives. He's healthy and ready to return to his job as a janitor at the local library.

More Stories From NPR

EXHIBIT 11

People With Intellectual And Developmental Disabilities More Likely To Die From Covid-19

Marla Milling Contributor ⓘ

Healthcare

I am a Forbes.com Contributor specializing in geriatric health and women's health articles.

A nurse pulls a suitcase as she helps a patient at Saint-Louis hospital in Paris, on May 28, 2020 as ... [+] AFP VIA GETTY IMAGES

Syracuse University and SUNY Upstate Medical University researchers recently analyzed more than 30,000 people who tested

positive for Covid-19 and found that those with intellectual and developmental disabilities (IDD) are more likely to die that those without IDD.

Breaking the data down by age group shows:

· Ages 0-17 – for every 100 people with Covid-19, 1.6 with IDD died compared to less than one without IDD

· Ages 18-74 – for every 100 people, 4.5 with IDD died; 2.7 without IDD

· Ages 75 and over – for every 100 people, 21.1 with IDD died; 20.7 without

"Based upon the case fatality rates we report among those ages 18-74, if 100,000 individuals with IDD contract Covid-19—which is entirely possible in light of the estimates of the size of this population and the cumulative incidence rates we are seeing in our research—we would expect 4,500 to die," says Scott Landes, associate professor of sociology at Syracuse University.

"Comparatively," he adds, "among 100,000 individuals without IDD, we would expect 2,700 to die. That would be an excess of 1,800 IDD deaths and in my mind that is unacceptable."

While the study did not investigate cause, the researchers noted that people with IDD had a higher prevalence of comorbid circulatory, respiratory and endocrine disease across all age groups.

They also say that there's a higher percentage of people with IDD who live in congregate settings.

"More attention is needed to this vulnerable health population in order to ensure their safety and well-being during this pandemic, including careful attention to the impact of public policies such as PPE (personal protective equipment) prioritization and funding streams on the ability of residential service providers to guarantee quality of care during this time," says Landes.

The study appears in Science Direct's *Disability and Health Journal*.

Follow me on Twitter or LinkedIn. Check out my website or some of my other work here.

Marla Milling

I am a full-time freelance writer in Asheville, North Carolina. I've written more than 900 published articles/essays for a wide variety of publications including...

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EXHIBIT 12

alzheimer's association®

2.3 MILLION CALIFORNIANS ARE LIVING WITH OR CARING FOR A LOVED ONE WITH ALZHEIMER'S OR DEMENTIA.

24/7 HELPLINE: 800.272.3900

The Alzheimer's Association is here all day, every day for people facing Alzheimer's and all dementia through our free 24/7 Helpline (800.272.3900) and website at alz.org. Support is available in 200 languages.

Coronavirus (COVID-19): Tips for Dementia Caregivers

Most likely, dementia does not increase risk for COVID-19, the respiratory illness caused by the new coronavirus, just like dementia does not increase risk for flu. However, dementia-related behaviors, increased age and common health conditions that often accompany dementia may increase risk.

For example, people with Alzheimer's disease and all other dementia may forget to wash their hands or take other recommended precautions to prevent illness. In addition, diseases like COVID-19 and the flu may worsen cognitive impairment due to dementia.

Tips for dementia caregivers at home

Caregivers of individuals living with Alzheimer's and all other dementia should follow guidelines from the Centers for Disease Control (CDC), and consider the following tips:

- For people living with dementia, increased confusion is often the first symptom of any illness. If a person living with dementia shows rapidly increased confusion, contact your health care provider for advice. Unless the person is having difficulty breathing or a very high fever, it is recommended that you call your health care provider instead of going directly to an emergency room. Your doctor may be able to treat the person without a visit to the hospital.
- People living with dementia may need extra and/or written reminders and support to remember important hygienic practices from one day to the next.
  - Consider placing signs in the bathroom and elsewhere to remind people with dementia to wash their hands with soap for 20 seconds.
  - Demonstrate thorough hand-washing.
  - Alcohol-based hand sanitizer with at least 60% alcohol can be a quick alternative to hand-washing if the person with dementia cannot get to a sink or wash his/her hands easily.
- Ask your pharmacist or doctor about filling prescriptions for a greater number of days to reduce trips to the pharmacy.
- Think ahead and make alternative plans for the person with dementia should adult day care, respite, etc. be modified or cancelled in response to COVID-19.
- Think ahead and make alternative plans for care management if the primary caregiver should become sick.

EXHIBIT 13

Management of physical health conditions in adults with severe mental disorders

WHO GUIDELINES

World Health Organization

Management of physical health conditions in adults with severe mental disorders

WHO GUIDELINES

World Health Organization

Guidelines for the management of physical health conditions in adults with severe mental disorders

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Acknowledgements

GUIDELINE DEVELOPMENT GROUP

Chair: Graham Thornicroft, King's College, London, United Kingdom.

Members: Abdullah Al-Khathami, Ministry of Health, Riyadh, Saudia Arabia; Christopher Dowrick, University of Liverpool, Liverpool, United Kingdom; Benjamin Druss, Emory University, Atlanta, USA; Rahib El Chammay, National Mental Health Programme, Beirut, Lebanon; Jacqueline Curtis, University of New South Wales, Sydney, Australia; Gail L. Daumit, Johns Hopkins University School of Medicine, Baltimore, USA; Christopher Dowrick, University of Liverpool, Institute of Psychology, Health and Society; Suhaila Ghuloum, Weill Cornell Medicine, Doha and Hamad Medical Corporation, Qatar; Oye Gureje, University College Hospital, Ibadan, Nigeria; Yueqin Huang, Peking University Institute of Mental Health, Beijing, China; Asma Humayun, Meditrina Healthcare, Islamabad, Pakistan; Mario Maj, University of Naples, Italy; Soontareeporn Meepring, Naresuan University, Bangkok, Thailand; Shanthi Mendis, Colombo, Sri Lanka; Thomas Munk Laursen, Aarhus University, Aarhus, Denmark; Dorairaj Prabhakaran, Public Health Foundation of India, New Delhi, India; Martin Prince, King's College London, London, United Kingdom; Thara Rangaswamy, Schizophrenia Research Foundation, Chennai, India; David Shiers, Psychosis Research Unit, Greater Manchester Mental Health Trust, UK and Division of Psychology and Mental Health, University of Manchester, UK; Ezra Susser, Columbia University, New York, USA; Abebaw Fekadu Wassie, College of Health Sciences, Addis Ababa University, Ethiopia.

Grade methodologist:
Corrado Barbui, University of Verona, Italy.

External review group: Atalay Alem, Department of Psychiatry, Faculty of Medicine, Addis Ababa University, Ethiopia; Zipporah Ali, Kenya Hospices and Palliative Care Association, Kenya; Lydia Chwastiak, University of Washington Medical Centre, USA; Alan Cohen, West London Mental Health Trust, UK; Pim Cuijpers, Virje University, Amsterdam, The Netherlands; Julian Eaton, London School of Hygiene and Tropical Medicine and CBM, UK; Alberto Minoletti, School of Public Health, Faculty of Medicine, University of Chile; Ayesha Motala, University of KwaZulu-Natal, South Africa; Rajat Ray, National Drug Dependence Treatment Centre, All India Institute of Medical Sciences, New Delhi, India; Sarrafzadegan Nizal, Isfahan University of Medical Sciences in Iran and School of Population and Public Health in the University of British Columbia in Canada; John Saunders, The University of Sydney, Australia; Najma Siddiqi, University of York, UK; Isolde Sommers, Danube University Krems, Austria; Charlene Sunkel, Central Gauteng Mental Health Society, South Africa; Héðinn Unnsteinsson, Prime Minister's Office, Iceland; Pieter Ventevogel, UNHCR, Switzerland Lakshmi Vijaykumar, Voluntary Health Services, Chennai, India; Inka Weissbecker, International Medical Corps, Washington DC, USA.

WHO STEERING GROUP

Overall coordination: Tarun Dua, Programme Manager, Department of Mental Health and Substance Abuse; Neerja Chowdhary, Technical Officer, Department of Mental Health and Substance Abuse.

WHO headquarters members: Bernadette Cappello, Department of Essential Medicines and Health Products; Meg Doherty, Department of HIV/AIDS; Alexandra Fleischmann, Department of Mental Health and Substance Abuse; Dongbo Fu, Department of Prevention of Noncommunicable Diseases; Ernesto Jaramillo, Global TB Programme; Dzmitry Krupchanka; Department of Mental Health and Substance Abuse; Shanthi Pal, Department of Essential Medicines and Health Products; Vladimir Poznyak, Department of Mental Health and Substance Abuse; Shekhar Saxena, Department of Mental Health and Substance Abuse; Mark van Ommeren, Department of Mental Health and Substance Abuse; Cherian Varghese, Department of NCDs, Disability, Violence and Injury Prevention. We also acknowledge the contribution of other colleagues: Marco Antonio De Avila Vitoria, Department of HIV/AIDS and Chantal Mignone, Department of HIV/AIDS.

WHO regional office advisors: Nazneen Anwar, WHO Regional Office for South-East Asia; Dan Chisholm, WHO Regional Office for Europe; Devora Kestel, WHO Regional Office for the Americas; Sebastiana Da Gama Nkomo, WHO Regional Office for Africa; Khalid Saeed, WHO Regional Office for the Eastern Mediterranean; Martin Vandendyck, WHO Regional Office for the Western Pacific.

WHO evidence review and synthesis team:
Jayati Das-Munshi, King's College London, London, United Kingdom; Petra Gronholm, King's College London, London, United Kingdom; Kavitha Kolappa, Harvard Medical School, Boston, USA; Maya Semrau, King's College, London and Brighton and Sussex Medical School, UK.

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Acronyms & abbreviation

AE	Adverse effect
ARV	Antiretroviral
CBT	Cognitive behaviour therapy
EMBASE	Excerpta Medica Database
GDG	Guideline Development Group
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HIC	High-income country
LMIC	Low- and middle-income country
MeSH	Medical Subject Headings
MD	Mean difference
MDR-TB	Multi drug resistant tuberculosis
mhGAP	Mental Health Gap Action Programme
NCD	Non-communicable diseases
OR	Odds ratio
PEN	Package of Essential Noncommunicable Disease Interventions
PICO	Population Intervention Comparison Outcome
RCT	Randomized controlled trial
RR	Relative risk
SMD	Severe mental disorders
SMR	Standardized mortality ratio

Executive summary

INTRODUCTION

The global burden of disease due to mental disorders continues to rise, especially in low- and middle-income countries (LMIC). In addition to causing a large proportion of morbidity, mental disorders – especially severe mental disorders (SMD) – are linked with poorer health outcomes and increased mortality. SMD are defined as a group of conditions that include moderate to severe depression, bipolar disorder, and schizophrenia and other psychotic disorders. People with SMD have a two to three times higher average mortality compared to the general population, which translates to a 10-20 year reduction in life expectancy. While people with SMD do have higher rates of death due to unnatural causes (accidents, homicide, or suicide) than the general population, the majority of deaths amongst people with SMD are attributable to physical health conditions, both non-communicable and communicable. Furthermore, people with SMD are more likely to engage in lifestyle behaviours that constitute risk factors for non-communicable diseases (NCDs) such as tobacco consumption, physical inactivity and consuming unhealthy diets.

Most studies reporting the excess mortality in people with SMD are from high income countries. The situation may be much worse in LMIC where the resources are inadequate, the institutions are not well managed and access to quality mental health care and physical care is limited.

Equitable access to comprehensive health services remains out of reach for the majority of people with SMD. Unfortunately, people with SMD often lack access to health services or receive poor quality care, including promotion and prevention, screening, and treatment. It is crucial to address the disparities in health care access and provision for people with SMD. Following the principle of non-discrimination and universal health coverage as elaborated in target 3.4 of the United Nations Sustainable Development Goals ("By 2030, reduce by one third premature mortality from non-communicable diseases through prevention and treatment and promote of mental health and well-being"), people with SMD should be offered at least the same level of treatment for physical health conditions and their risk factors as the general population.

The WHO *Comprehensive Mental Health Action Plan (2013-2020)* outlines a vision where people living with mental disorders are able to exercise the full range of human rights and to access high quality, culturally-appropriate health and social care in a timely way to promote recovery. In service of this vision and as part of WHO's Mental Health Gap Action Programme (mhGAP), these *Guidelines on the management of physical health conditions in adults with severe mental disorders* will provide up-to-date, evidence-based recommendations to support the scale-up of care for physical health conditions and their risk factors affecting people living with SMD globally.

Accordingly, the objective of these guidelines is:

To improve the management of physical health conditions in adults with SMD and support the reduction of individual health behaviours constituting risk factors for these illnesses, with the aim of decreasing morbidity and premature mortality amongst people with SMD.

Existing WHO guidelines for the general population are relevant to the physical health conditions that increase the morbidity and mortality for people with SMD. For example, the *Package of Essential Noncommunicable (PEN) Disease Interventions for Primary Health Care in Low-Resource*

Settings Geneva, WHO, 2010 provides guidelines and recommendations for tobacco cessation, weight management, cardiovascular disease prevention including diabetes management and prevention of complications, treatment and prevention of chronic respiratory diseases in the general population. Other WHO guidelines for infectious disease are also relevant such as the *Consolidated guidelines on HIV prevention, diagnosis, treatment, and care for key populations. WHO, 2016 update* and *Guidelines for treatment of drug-susceptible tuberculosis and patient care, 2017 update. WHO, 2017.*

GUIDELINE DEVELOPMENT METHODS

The process of development of these guidelines followed the *WHO handbook for guideline development* and involved: (1) recruitment of the Guideline Development Group (GDG); (2) declaration of interest by GDG members and peer reviewers; (3) scoping review to formulate questions and select outcomes (4) identification, appraisal and synthesis of available evidence; (5) formulation of recommendations with inputs from a wide range of stakeholders; and (6) preparation of documents and plans for dissemination.

The GDG, an international group of experts, provided input into the scope of the guideline and assisted the steering group in developing the key questions. A total of one background question and seven PICO (Population, Intervention, Comparison, and Outcome) questions were developed.

To address the PICO questions, a series of searches for systematic reviews was conducted and GRADE evidence profiles prepared. During a meeting at WHO headquarters in Geneva, 9 – 10 May 2018, the GDG discussed the evidence, sought clarifications, and interpreted the findings in order to develop recommendations. The GDG considered the relevance of the recommendations for people with SMD including the balance of benefit and harm of each intervention; values and preferences of people with SMD; costs and resource use; and other relevant practical issues for providers in LMIC.

When making a strong recommendation, the GDG was confident that the desirable effects of the intervention outweigh any undesirable effects. When the GDG was uncertain about the balance between the desirable and undesirable effects, the GDG issued a conditional recommendation. Strong recommendations imply that most individuals would want the intervention and should receive it while conditional recommendations imply that different choices may be appropriate for individual people and they may require assistance at arriving at management decisions. The GDG members reached an unanimous agreement on all the recommendations and ratings.

SUMMARY OF RECOMMENDATIONS

Tobacco cessation

In the context of tobacco cessation programmes:

Recommendation 1:
In people with severe mental disorders, combined pharmacological and non-pharmacological interventions may be considered in accordance with the WHO training package (*Strengthening health systems for treating tobacco dependence in primary care. Building capacity for tobacco control: training package*). *(Strength of recommendation: Conditional; quality of evidence: Very low).*

Recommendation 2:
In people with severe mental disorders, a directive and supportive behavioural intervention programme may be considered and should be tailored to the needs of the population. *(Strength of recommendation: Conditional; quality of evidence: Very low).*

Recommendation 3:
In people with severe mental disorders, varenicline, bupropion and nicotine replacement therapy may be considered for tobacco cessation. *(Strength of recommendation: Conditional; quality of evidence: Very low).*

BEST PRACTICE STATEMENT:
Prescribers should take into account potential interactions between buproprion and varenicline with psychotropic medications as well as possible contra-indications.

Weight management

Recommendation 1:
Behavioural lifestyle (healthy diet, physical activity) interventions should be considered in all people with severe mental disorders who are overweight or obese or at risk of becoming overweight or obese in accordance with *WHO's Package of Essential Noncommunicable Disease Interventions (WHO PEN) for primary care in low-resource settings (2010).* These interventions should be appropriate and tailored to the needs of this population. *(Strength of recommendation: Strong; Quality of evidence: Very low).*

Recommendation 2:
For people with severe mental disorders who are overweight or obese, and where lifestyle interventions and/or switching psychotropic medication do not appear successful, adjunctive metformin may be considered. This should be considered under close clinical supervision and monitoring.
(Strength of recommendation: Conditional; Quality of evidence: Low).

BEST PRACTICE STATEMENTS:

- For people with severe mental disorders who are overweight or obese or at risk of becoming overweight or obese, initiating a psychotropic medication with lower propensity for weight gain should be considered, taking into account clinical benefits and potential adverse effects.
- For people with severe mental disorders who are overweight or obese, switching to a psychotropic medication with a lower propensity for weight gain may be considered, taking into account clinical benefits and potential adverse effects.

Substance use disorders

Recommendation 1:

For people with severe mental disorders and comorbid substance use disorders (drug and/or alcohol), interventions should be considered in accordance with the WHO mhGAP guidelines. *(Strength of recommendation: Conditional; Quality of the evidence: Low).*

Recommendation 2:

Non-pharmacological interventions (e.g. motivational interviewing) may be considered and tailored to the needs of people with severe mental disorders and substance use disorders *(Strength of recommendation: Conditional; Quality of the evidence: Very low).*

BEST PRACTICE STATEMENT:

Prescribers should take into account the potential for drug-drug interactions between medicines used for treatment of substance use disorders and severe mental disorders.

Cardiovascular disease and cardiovascular risk

Recommendation 1:

For people with severe mental disorders and pre-existing cardiovascular disease, or with cardiovascular risk factors (e.g. high blood pressure or high cholesterol), pharmacological and non-pharmacological interventions may be considered in accordance with the *WHO Package of Essential Noncommunicable Disease Interventions (WHO PEN) for primary care in low-resource settings (2010)* for lowering cardiovascular risk and management of cardiovascular disease.
(Strength of recommendation: Strong; Quality of evidence: High to moderate for different interventions).

Recommendation 2:

For people with severe mental disorders and pre-existing cardiovascular disease, the following is recommended:

a) Behavioural lifestyle (healthy diet, physical activity) interventions may be considered. These interventions should be appropriate and tailored to the needs of this population. *(Strength of recommendation: Conditional; Quality of evidence: Very low).*

b) Collaborative care i.e. a multi-professional approach to patient care with a structured management plan, scheduled patient follow-up, and enhanced inter-professional communication, may be considered for cardiovascular disease management. *(Strength of recommendation: Conditional; Quality of evidence: Very low).*

Recommendation 3:

For people with severe mental disorders and cardiovascular risk factors, behavioural lifestyle (healthy diet, physical activity) interventions may be considered. These interventions should be appropriate and tailored to the needs of this population. *(Strength of recommendation: Conditional; Quality of evidence: Very low).*

BEST PRACTICE STATEMENTS:

For people with severe mental disorders and pre-existing cardiovascular disease:

- Initiating a psychotropic medication with lower propensity for cardiovascular risk is a strategy that should be considered, taking into account clinical benefits and potential adverse effects.
- Switching to a psychotropic medication with lower propensity for cardiovascular risk may be considered, taking into account clinical benefits and potential adverse effects.

For people with severe mental disorders and pre-existing cardiovascular disease or cardiovascular risk factors:

- Prescribers should be aware of potential interactions between prescribed medicines for cardiovascular disease and prescribed psychotropic medications, which may affect cardiovascular risk. Cardiovascular outcomes and risk factors should be monitored and dose adjustment of cardiovascular medicines may be required.

Diabetes mellitus

Recommendation 1:
For people with severe mental disorders and diabetes mellitus, interventions in accordance with the WHO Package of Essential Non-communicable (PEN) Disease Interventions for Primary Health Care in Low-Resource Settings should be considered for diabetes management.
(Strength of recommendation: Strong; Quality of evidence: Low).

Recommendation 2:
Behavioural lifestyle interventions should be considered for all people with severe mental disorders and diabetes mellitus. These interventions should be appropriate and tailored to the needs of this population.
(Strength of recommendation: Strong; Quality of evidence: Very low).

Recommendation 3:
In people with depression and comorbid diabetes mellitus, cognitive behaviour therapy for treatment of depression may be considered. *(Strength of recommendation: Conditional; Quality of evidence: Very low).*

BEST PRACTICE STATEMENTS:

For people with severe mental disorders and diabetes mellitus:

- Initiating an anti-psychotic medication with lower propensity for producing hyperglycaemia should be considered, taking into account clinical benefits and potential adverse effects.
- Switching to an anti-psychotic medication with lower propensity for producing hyperglycaemia is a strategy that may be considered, taking into account clinical benefits and potential adverse effects.
- Prescribers should be aware of potential interactions between prescribed medicines for diabetes mellitus and prescribed psychotropic medicines, which may affect glycaemic control. Glycaemic control should be monitored and dose adjustment of medicines may be required.

HIV/AIDS

Recommendation 1:
For people with severe mental disorders and HIV/ AIDS, antiretroviral drugs should be considered in accordance with the *WHO Updated recommendations on first-line and second-line antiretroviral regimens. (Strength of the recommendation: Strong; Quality of the evidence: Moderate)*

Recommendation 2:
Additional psychosocial support for treatment adherence should be provided to people with HIV and severe mental disorders in accordance with the *WHO consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection. (Strength of the recommendation: Strong; Quality of the evidence: Moderate)*

BEST PRACTICE STATEMENT:
For people with severe mental disorders and HIV/ AIDS, prescribers should take into account the potential for drug-drug interactions between antiretroviral drugs and psychotropic medicines.

Other infectious diseases (Tuberculosis, Hepatitis B/C)

Recommendation 1:
For people with severe mental disorders and TB, pharmacological management should be considered in accordance with the *WHO guidelines for the treatment of drug-susceptible tuberculosis and patient care* and the *WHO treatment guidelines for drug-resistant tuberculosis.*
(Strength of the recommendation: Strong; Quality of the evidence: Low).

Recommendation 2:
For people with severe mental disorders and TB, non-pharmacological (social, psychological) management should be considered in accordance with the *WHO guidelines for the treatment of drug-susceptible tuberculosis and patient care* and the *WHO treatment guidelines for drug-resistant tuberculosis.*
(Strength of the recommendation: Strong; Quality of the evidence: Low).

Recommendation 3:
For people with severe mental disorders and hepatitis B, treatment should be considered in accordance with the *WHO guidelines for the prevention, care and treatment of persons with chronic hepatitis B infection.*
(Strength of the recommendation: Strong; Quality of the evidence: Low).

Recommendation 4:
For people with severe mental disorders and hepatitis C, treatment should be considered in accordance with the *WHO guidelines for the screening care and treatment of persons with chronic hepatitis C infection.*
(Strength of the recommendation: Strong; Quality of the evidence: Low).

BEST PRACTICE STATEMENT:
For people with severe mental disorders and TBand/or Hepatitis B/, prescribers should take into account the potential for drug-drug interactions between TB medicines, medicines for hepatitis B and C with psychotropic medicines.

1. Introduction

1.1 BACKGROUND AND RATIONALE

Worldwide, mental disorders contribute to 7% of the global burden of disease as estimated by disability adjusted life years and this is rising especially in low- and middle- income countries (LMIC) (GBD 2016). In addition to causing a large proportion of morbidity, mental disorders – especially severe mental disorders (SMD) – are linked with poorer health outcomes and increased mortality. SMD are defined as a group of conditions that include moderate to severe depression, bipolar disorder, and schizophrenia and other psychotic disorders. People with SMD have a 2-3 times higher average mortality compared to the general population, which translates to a 10-20 year reduction in life expectancy (Liu *et al.*, 2017). People with bipolar disorder and schizophrenia have been shown to have higher rates of mortality in both high and low-income settings (Tsuang, Woolson and Fleming, 1980) (Capasso *et al.*, 2008) (Laursen, 2011) (Nielsen *et al.*, 2013) (Fekadu *et al.*, 2015). One prospective cohort-study in Ethiopia found the overall standardized mortality ratio (SMR) of people with SMD to be twice that of the general population, with schizophrenia associated with the highest risk (SMR three times that of the general population) (Fekadu *et al.*, 2015). Moreover, for schizophrenia in particular, the mortality gap appears to be widening over time (Saha, Chant and McGrath, 2007).

Numerous potential causes have been proposed for the increased mortality of people with SMD, including the well-known evidence-based bidirectional relationship between mental disorders and other non-communicable diseases (NCDs) such as cardiovascular disease, diabetes, respiratory illnesses, and cancers; differential exposure to risk factors driving the aforementioned NCDs such as smoking, harmful use of alcohol, and sedentary behaviour; iatrogenic effects of medications for SMD; and inequitable access to health care services. While people with SMD do have higher rates of death due to unnatural causes (accidents, homicide, or suicide) than the general population, the majority of deaths amongst people with SMD are attributable to physical health conditions, both non-communicable and communicable (Liu *et al.*, 2017). Cardiovascular disease, for example, confers a ten-fold higher risk of death than suicide in people with SMD. Overall, people with SMD have approximately 1.5-3 times higher risk of cardiovascular morbidity and mortality when compared with the general population (Correll *et al.*, 2017). People with SMD also have higher rates of diabetes mellitus (Vancampfort *et al.*, 2016), with reports of a 2-3 fold higher prevalence compared with the general population. Infectious diseases such as HIV/AIDS also contribute to the high rates of premature death amongst people with SMD, as do other infectious diseases such as tuberculosis and hepatitis B and C (Saha, Chant and McGrath, 2007).

The figures mentioned above are chiefly drawn from studies from high income countries where health literacy is higher, better quality services are available, and there is overall better monitoring of the institutions and more regular check-ups for physical health of people with SMD. The situation may be much worse in LMICs where the resources are inadequate, the institutions are not well managed and access to quality mental health care and physical care is limited.

SMD can affect and in turn, can be affected by NCDs. People with SMD are also more likely to engage in lifestyle behaviours that constitute risk factors for NCDs. Tobacco consumption (Lasser *et al.*, 2000) is common amongst people with SMD and has been identified as a leading preventable cause of premature mortality in this population. Additionally, people with SMD are more likely to be physically inactive and consume unhealthy diets (Jakobsen *et al.*, 2018), increasing their risk of being overweight or obese. In routine clinical practice, however, such comorbidities and interactions are often overlooked.

Iatrogenic effects of psychotropic medications that are used to treat the symptoms of SMD including antipsychotic medication (and to some extent, antidepressants and mood stabilizers) are also associated with an increased risk of developing physical health conditions and associated complications (Correll *et al.*, 2015) (Correll *et al.*, 2017).

Furthermore, equitable access to comprehensive health services remains out of reach for many people with SMD. Unfortunately, people with SMD often lack access to health services or receive poor quality care, including promotion and prevention, screening, and treatment (De Hert *et al.*, 2011). The socioeconomic disadvantages not least due to the stigma and discrimination associated with SMD may further influence affected people's health and health care (Lund *et al.*, 2013). In addition, although families and other informal carers may provide vital practical help to deal with complex comorbidities and navigate health systems, they can be left to struggle under intense stress and with little support themselves (Poon *et al.*, 2017). It is therefore crucial to address the disparities in health care access and provision for people with SMD.

Following the principle of non-discrimination and universal health coverage as elaborated in target 3.4 of the United Nations Sustainable Development Goals ("By 2030, reduce by one third premature mortality from non-communicable diseases through prevention and treatment and promotion of mental health and well-being"), people with SMD should be offered at least the same level of treatment for physical health conditions and their risk factors as the general population. In some instances, as these guidelines will elaborate further, treatment recommendations for the general population need to be adapted for people with SMD. The benefits and risks of pharmacological interventions need to be balanced against the potential side effects and drug-drug interactions commonly used for SMD. People with SMD often experience impairment in functioning which makes it difficult for them to take the initiative to access health care, to keep appointments or to take medications for physical health conditions as prescribed. Non-pharmacological interventions need to be tailored according to the cognitive, motivational and socio-cultural needs of people with SMD.

Recognizing the frequent comorbidity between mental and physical health conditions, specific recommendations addressing the physical conditions causing the increased morbidity and mortality of people with SMD are needed. These new WHO guidelines constitute an important step in providing better health care for people with SMD, and offer up-to-date, evidence-based recommendations for the management of these physical health conditions and reduction of their risk factors for people with SMD. While these guidelines do not include a comprehensive list of physical health conditions, but have rather focused on those that seemed most important and for which there was evidence available, the physical health conditions (and their risk factors) addressed are those that have been shown to increase morbidity and mortality in people with SMD. It is hoped that these guidelines will benefit people with SMD whose physical health may currently be neglected and may contribute to reduced premature mortality amongst this population.

These guidelines will help achieve the United Nations Sustainable Development Goals 3.4, and facilitate the implementation of *WHO's Comprehensive Mental Health Action Plan* (World Health Organization, 2013). The guidelines build upon prior work by WHO Headquarters and Regional Offices. The WHO Regional Office for Europe published a technical report titled, *Addressing comorbidity between mental disorders and major noncommunicable diseases*, to support implementation of the *WHO European Mental Health Action Plan 2013-2020* and the *WHO European Action Plan for the Prevention and Control of Noncommunicable Diseases 2016-2025* (World Health Organization Regional Office for Europe, 2016). Additionally, the WHO Department of Mental Health and Substance Use Disorder held a consultation on excess mortality in people with SMD with key international experts in December 2015 (World Health Organization, 2015). This consultation included discussions on physical health conditions and the risk factors responsible for excess mortality in this population and the need for evidence-based guidance was recognized.

1.2 RELATED WHO GUIDELINES AND TOOLS

Several existing WHO guidelines and tools designed for the general population are relevant for addressing the physical health conditions and their risk factors causing the increased morbidity and mortality of people with SMD. These were consulted in the guideline development process (Box 1); recommendations were either added or modified for this special population, using targeted evidence reviews and expert opinions to assess the applicability of data for the general population to people with SMD.

1.3 TARGET AUDIENCE

These guidelines are primarily intended for use by health care workers providing services for people with SMD at all levels of the health care system, including outpatient and inpatient care at first-level, second-level, district and tertiary healthcare facilities. Health care providers may include primary care doctors, nurses, specialists, or other members of the health care work force.

In addition, these guidelines are of interest to the following audiences:

- Policy makers and health care planners at the national and local levels
- National and regional mental health programme managers
- National and regional primary care programme managers
- Members of national and local health departments
- People living with SMD and their families
- Groups representing people with SMD and their families

BOX 1: Related WHO guidelines and tools:

1. *Mental Health Gap Action Programme (mhGAP) Intervention Guide for mental, neurological, and substance use disorders in non-specialized health settings (Version 2.0). Geneva, WHO, 2016.* http://www.who.int/mental_health/mhgap/mhGAP_intervention_guide_02/en/
2. *Package of Essential Noncommunicable (PEN) Disease Interventions for Primary Health Care in Low-Resource Settings. Geneva, WHO, 2010.* http://www.who.int/cardiovascular_diseases/publications/pen2010/en/
3. *Strengthening health systems for treating tobacco dependence in primary care. Building capacity for tobacco control: training package.* http://www.who.int/tobacco/publications/building_capacity/training_package/treatingtobaccodependence/en/
4. *Global recommendations on physical activity for health. Geneva, WHO, 2010.* http://www.who.int/dietphysicalactivity/publications/9789241599979/en/
5. *Consolidated guidelines on HIV prevention, diagnosis, treatment, and care for key populations. Geneva, WHO, 2016 update.* http://www.who.int/hiv/pub/guidelines/keypopulations-2016/en/
6. *Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection.Recommendations for a public health approach. Second edition. Geneva, WHO, 2016.* http://www.who.int/hiv/pub/arv/arv-2016/en/
7. *WHO guidelines for the treatment of drug-susceptible tuberculosis and patient care* (http://apps.who.int/iris/bitstream/handle/10665/255052/9789241550000-eng.pdf?sequence=1)
8. *WHO treatment guidelines for drug-resistant tuberculosis* (http://apps.who.int/iris/bitstream/handle/10665/250125/9789241549639-eng.pdf?sequence=1).
9. *Guidelines for the prevention, care, and treatment of persons with chronic hepatitis B infection. Geneva, WHO, 2015.* http://www.who.int/hepatitis/publications/hepatitis-b-guidelines/en/
10. *Guidelines for the screening, care, and treatment of persons with chronic hepatitis C infection. Geneva, WHO, 2016.* http://www.who.int/hepatitis/publications/hepatitis-c-guidelines-2016/en/

1.4
GOAL AND OBJECTIVE

The *WHO Comprehensive Mental Health Action Plan* (2013-2020) outlines a vision where persons living with mental disorders are able to exercise the full range of human rights and to access high quality, culturally-appropriate health and social care in a timely way to promote recovery (World Health Organization, 2013). In service of this vision and as part of *WHO's Mental Health Gap Action Programme (mhGAP)*, these guidelines provide up-to-date, evidence-based recommendations to support improved access to quality care for physical health conditions and to address the risk factors affecting people living with SMD globally. They will be consistent with services oriented towards recovery and focus on the strengths of people with SMD. Accordingly, the objective of these guidelines is:

- To improve the management of physical health conditions in adults with SMD and support the reduction of individual health behaviours constituting risk factors for these illnesses, with the aim of decreasing morbidity and premature mortality amongst people with SMD.

1.5
GUIDING PRINCIPLES

The following principles have informed the development of these guidelines and should guide the implementation of their recommendations:

- The guidelines should expedite the achievement of the goals outlined in the *Mental Health Action Plan (2013-2020)*(World Health Organization, 2013), as well as Goal 3.4 of the Sustainable Development Goals, which focuses on reducing the premature mortality from non-communicable diseases and the promotion of mental health and well-being (United Nations, 2016).

- The process of developing these guidelines and subsequent implementation of recommendations should further the realization of the right to equal levels of health for people living with SMD and promote their active involvement.

- The recommendations should be implemented with accompanying efforts to safeguard the human rights of persons living with SMD, including reduction of stigma, reducing barriers to seeking health services, and ensuring informed decision-making in treatment choices.

Implementation of the recommendations should be informed by the local context, including the availability of financial and human resources. However, the inequities addressed in these guidelines are common across all countries, and should be made a priority in health services.

2. Guideline development process

The *WHO handbook for guideline development*, 2nd edition (http://apps.who.int/medicinedocs/documents/s22083en/s22083en.pdf) describes the process used in the development of these guidelines, following the steps below.

2.1 GUIDELINE DEVELOPMENT GROUP

A WHO guideline steering group, led by the Department of Mental Health and Substance Use Disorder, was established with representatives from WHO regional offices and relevant WHO departments and programmes. The guideline steering group provided overall support to the guideline development process. Two additional groups were established: a guideline development group (GDG) and an external review group. The GDG included a panel of academics and clinicians with multidisciplinary expertise on the conditions covered by the guidelines. Consideration was given to geographic diversity and gender balance (see Annex 1).

Potential members of the GDG were selected on the basis of their contribution to the area, as well as the need for regional and area of expertise diversity. As a respected researcher in the field, the Chairperson was selected for his extensive experience of guideline development methodology, and his participation in other guideline development groups. Each potential GDG member was asked to complete the WHO declaration of interest (DOI) form. These were reviewed by the steering group.

2.2 DECLARATIONS OF INTEREST AND MANAGEMENT OF CONFLICTS OF INTEREST

All GDG members, peer reviewers and systematic review team members were requested to complete the declaration of interest (DoI) form prior to the evidence review process for guideline development. Invitations to participate in the GDG meeting were sent only after the DoI had been reviewed and approved. The GDG members were also required to complete a confidentiality undertaking. Once received, the WHO Secretariat reviewed the DoIs as well as additional information (internet and bibliographic database search) and evaluated if there are any conflicts of interest and if so, whether these require a management plan. The group composition was finalized after this process.

In order to enhance its management of conflicts of interest as well as strengthen public trust and transparency in connection with WHO meetings and activities involving the provision of technical/normative advice, the names and brief biographies of members being considered for participation in the GDG were disclosed for public notice and comment prior to the meeting.

At the beginning of the GDG meeting, the DoI of each GDG member was presented and GDG members and external partners were asked to update their DoI with relevant changes by notifying the WHO Secretariat.

DoI were reassessed for potential conflict before the face-to-face meeting in Geneva. None of the members had major conflicts of interest. All decisions were documented (see Annex 2).

2.3 COLLABORATION WITH EXTERNAL PARTNERS

The Centre for Global Mental Health, Institute of Psychiatry, Psychology & Neuroscience, King's College London, UK (WHO Collaborating Centre for Research and Training in Neurosciences) supported the development of the guidelines by conducting the evidence review and synthesis.

2.4 IDENTIFYING, APPRAISING AND SYNTHESIZING AVAILABLE EVIDENCE

A scoping review helped to identify the key questions that would establish the focus of the recommendations and consisted of the following steps:

1) Initial broad focus on identification of risk factors for excess mortality and morbidity in people with SMD and specific interventions, guided by previous work by the WHO that has highlighted a number of physical health conditions and associated risk factors as critical factors in the excess mortality and morbidity in people with SMD;

2) Review of existing WHO guidelines;

3) Findings of the WHO consultation on the above topic and other relevant WHO documents and discussions with WHO steering group.

A total of one background question and seven key questions in PICO (Population, Intervention, Comparison, and Outcome) format were developed (Annex 3).

The background question provided the context and rationale for the guidelines and addressed the association of physical health conditions with SMD. It consisted of two sub-questions: *What is the comorbidity between physical health conditions (NCDs and infectious diseases) and SMD? What is the impact of physical health conditions on the morbidity and mortality of people with SMD?* The answer to this question was found in a wide range of information sources and summarised the growing body of evidence that has demonstrated the bi-directional relationships between SMD and physical health conditions. The evidence supporting the background question is presented in Annex 4.

Outcomes were rated by GDG members according to their importance as 'critical' for a decision, 'important' or 'unimportant'. Those outcomes rated as critical and important were selected for inclusion into the PICO questions. Regular communication and discussions with the GDG were held by email and teleconferences, respectively.

The WHO steering group, in consultation with the guideline methodologist and GDG chair, proposed a framework based on the PICO questions to review the evidence. The process entailed the following steps: (i) review of evidence that exists for the interventions to manage physical health conditions in people with SMD; (ii) examination of the extent to which existing recommendations for the general population (especially from existing WHO guidelines) can be applied to people with SMD; (iii) examination of when and how these recommendations need to be adapted for people with SMD; and (iv) to provide recommendations that are specific to this population when needed.

The systematic review team developed protocols to review the evidence that existed for the interventions to manage physical health conditions and their risk factors (as outlined in the PICO questions) for people with SMD (Annex 5). Existing relevant systematic reviews were identified for each of the PICO questions. The steering group assessed the quality of existing reviews using the assessment of multiple systematic reviews (AMSTAR) checklist. Systematic reviews found to be of high quality were also assessed for timeliness to ensure that the most current evidence was used. In addition, drug-drug interaction searches were conducted between medicines relevant for each PICO question and medicines used for SMD (Annex 5).

The Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology (Guyatt *et al.*, 2011) was used to develop the evidence profiles as well as the WHO Handbook for Guideline Development. The quality assessment of the evidence was performed according to GRADE considering study design (randomized controlled trials or observational studies), risk of bias, inconsistency, indirectness, imprecision and risk of reporting bias. Evidence was characterised as either high, moderate, low or very low. The evidence profiles are available at the WHO website (http://www.who.int/mental_health/evidence/guidelines_physical_health_and_severe_mental_disorders/en/index.html).

2.5 DECISION-MAKING DURING THE GUIDELINE DEVELOPMENT GROUP MEETING

The GDG met at the WHO headquarters in Geneva, 9 – 10 May 2018. The evidence reviews were sent out in advance and summarized in a presentation during the meeting. The GDG members discussed the evidence, clarified points, and interpreted the findings in order to develop recommendations based on the draft prepared by the WHO Secretariat. The GDG considered the relevance of the recommendations for people with SMD based on the GRADE-DECIDE framework (Alonso-Coello *et al.*, 2016):

- the balance of benefit and harm of each intervention;
- values and preferences of people with SMD and their carers;
- costs and resource use;
- acceptability of the intervention to healthcare providers in low- and middle-income countries;
- feasibility of implementation;
- impact on equity and human rights.

The discussion and assessment of values and preferences was based on the knowledge and experience of GDG members. Similarly, no surveys or formal cost-effectiveness studies to determine resource constraints were conducted but discussions of these domains were informed by the combined expertise and experience of the GDG members. Equity and human rights were considered by specifically searching databases that include studies from LMIC, examining data for disaggregation for specific subgroups of people with SMD and when direct evidence for the relevant subgroup was not available, evaluating the indirectness of evidence obtained from other populations. Potential differential effects of the interventions on different subgroups of people with SMD related to economic status, employment or occupation, education, place of residence, gender or ethnicity were considered by the GDG. Equity and human rights considerations were applied to the other criteria in the framework described above by:

- assessing both desirable and undesirable effects for different subgroups of people with SMD;
- examining if some subgroups may value the main outcomes differently than the general population;
- balancing treatment costs with effectiveness;
- varied acceptability of the intervention in different subgroups.

Taking into account these considerations, when making a strong recommendation, the GDG was confident that the desirable effects of the intervention outweighs any undesirable effects. When the GDG was uncertain about the balance between the desirable and undesirable effects, the GDG issued a conditional recommendation. Strong recommendations imply that most individuals would want the intervention and should receive it while conditional recommendations imply that different choices may be appropriate for individual patients and they may require assistance at arriving at management decisions. In some instances even when the quality of evidence was low or very low, it was agreed that if the recommendation would be of general benefit, and this was seen to outweigh the harms, it

may still be rated as strong. In the event of a disagreement, the chair and the methodologist would ascertain whether the dispute was related to the interpretation of the data or to the way that the recommendation was formulated. If a consensus agreement was not reached, the GDG members agreed to a majority vote of 70% to determine a decision The WHO staff members present at the meeting, as well as other external technical experts involved in the collection and review of the evidence, were excluded from voting. The GDG members reached a consensus agreement on all recommendations and ratings and voting was not needed.

In addition to recommendations, best practice statements were formulated which did not rely on systematic reviews of the evidence but rather on good clinical care and were consensus-based from the GDG.

2.6 DOCUMENT PREPARATION AND PEER REVIEW

In addition to the GDG members, an external review group (ERG) provided expert inputs. The draft guideline and evidence profiles prepared by WHO staff and the GDG were circulated to the external review group and the steering group. The role of the ERG was to identify any errors or missing data and to comment on clarity, setting–specific issues and implications for implementation rather than changing the recommendations. All inputs and remarks were discussed and agreed with the GDG by email.

3. Evidence and recommendations

This section provides an overview of each PICO question described under the following headings: the background; recommendations and additional considerations; supporting evidence for the recommendations and the rationale for the recommendations based on the evidence synthesized as well as criteria listed in the evidence-to-decision tables. The complete evidence profiles for each PICO question including the GRADE tables and the evidence-to-decision tables are available online on the WHO website (http://www.who.int/mental_health/evidence/guidelines_physical_health_and_severe_mental_disorders/en/index.html). Annex 6 has the drug-drug interaction evidence between medicines relevant for each PICO question and medicines used for SMD.

3.1 TOBACCO CESSATION

For people with SMD who use tobacco, are pharmacological (including nicotine replacement therapy, bupropion, varenicline) and/or non-pharmacological interventions effective to support tobacco cessation?

Population:
People with SMD who use tobacco

Intervention:
- Pharmacological interventions: including nicotine replacement therapy (NRT), bupropion, varenicline
- Non-pharmacological interventions

Comparison:
Care as usual and/or placebo

Outcomes:
- Critical
  - Tobacco cessation/abstinence rates
  - Tobacco consumption rates
  - Respiratory disease outcomes (COPD, asthma)
- Important
  - Frequency of adverse events/side-effects

BACKGROUND

People with SMD are twice as likely to use tobacco as the general population (around 61% of people with SMD smoke compared to 33% in the general population), to smoke more on average, and are less likely to quit smoking (Centers for Disease Control and Prevention, 2015). People with SMD have been reported to die 15-20 years earlier on average than people in the general population and this is often due to preventable tobacco-related health conditions for example due to heart disease, cancer, and lung disease, which can all be caused by smoking (Trainor and Leavey, 2017). Nicotine has also been shown to have mood-altering effects that can temporarily mask the negative symptoms of mental disorder, putting people with mental disorder at higher risk for cigarette use and nicotine addiction, and tobacco smoke can interact with and inhibit the effectiveness of certain medications taken for mental health conditions and substance abuse (https://www.cdc.gov/tobacco/disparities/mental-illness-substance-use/index.html).

In regard to interventions that have been recommended in the general population for tobacco cessation, bupropion, varenicline and nicotine replacement therapy (NRT) have all been recommended (e.g. mhGAP Intervention Guide, The National Institute for Health and Care Excellence (NICE)), and NICE has also recommended these pharmacological interventions for tobacco cessation for people with mental disorders (NICE guidelines CG178, CG185, CG91. PH48).

RECOMMENDATIONS AND CONSIDERATIONS

In the context of tobacco cessation programmes:

RECOMMENDATION 1:

In people with severe mental disorders, combined pharmacological and non-pharmacological interventions may be considered in accordance with the WHO training package (Strengthening health systems for treating tobacco dependence in primary care. Building capacity for tobacco control: training package) (http://www.who.int/tobacco/publications/building_capacity/training_package/treatingtobaccodependence/en/).

(Strength of recommendation: Conditional; quality of evidence: Very low)

RECOMMENDATION 2:

In people with severe mental disorders, a directive and supportive behavioural intervention programme may be considered and should be tailored to the needs of the population.

(Strength of recommendation: Conditional; quality of evidence: Very low)

RECOMMENDATION 3:

In people with severe mental disorders, varenicline, bupropion and nicotine replacement therapy may be considered for tobacco cessation.

(Strength of recommendation: Conditional; quality of evidence: Very low)

BEST PRACTICE STATEMENT:

Prescribers should take into account potential interactions between buproprion and varenicline with psychotropic medications as well as possible contra-indications.

Additional considerations

- Tobacco cessation interventions should be considered as part of broader implementation packages as described in *WHO's MPOWER* (WHO., 2008) package of effective tobacco control measures.
- The behavioral intervention programme can build on the WHO training package and should be tailored to the needs of the population. This is based on the principles of motivational interviewing and aims to increase the person's intrinsic motivation for change based on the person's own personal goals and values.
- Choice of pharmacotherapy will be understandably influenced by resource availability. In people with SMD, varenicline seems to have the highest efficacy, followed by bupropion with or without nicotine replacement therapy, followed by nicotine replacement therapy (nicotine patch) alone.
- Smoking cessation can cause an increase in serum levels of anti-psychotic medication, and smoking cessation needs to be accompanied by a reduction in dose to avoid toxicity. Smoking cessation programmes therefore need to be accompanied by monitoring of clinical state, and where appropriate monitoring of serum levels.

SUPPORTING EVIDENCE AND RATIONALE

Behavioural treatment alone for tobacco smoking cessation has a low abstinence rate in SMD of about 4% which is why combination behavioural treatment and pharmacotherapy is recommended for the population with SMD. At present there is insufficient evidence to indicate whether specialised smoking cessation interventions (vs. standard smoking cessation) and contingent reinforcement i.e. a positive reinforcement technique to increase desired behaviours, in this case tobacco cessation (vs. care as usual) are beneficial for the cessation of smoking in people with SMD. Varenicline's efficacy has been shown to be the highest of the pharmaco-therapy choices for persons with SMD including when compared to bupropion(Anthenelli *et al*., 2016). Evidence for efficacy of bupropion comes from several studies included in the Cochrane review such as the EAGLES trial (Tsoi, 2013); evidence for efficacy of nicotine patch vs. placebo can be seen in the EAGLES trial. While there are no known interactions between NRT or varenicline and medicines used for SMD, there are multiple interactions between bupropion and medicines used for SMD, specifically involving elevated seizure risk and enzymatic inhibition/induction. There is some evidence that people taking buproprion, and varenicline may have increased risk of neuropsychiatric symptoms.

Although the evidence specifically for people with SMD is limited with few studies of small size, WHO has comprehensive tools for tobacco cessation in the general population and the GDG agreed that there was no suggestion of inconsistency with the evidence for tobacco cessation interventions in the general population and in people with SMD. The GDG agreed that the benefits of the interventions outweighed the harms while recognising that prescribers should take into account potential interactions between buproprion with psychotropic medications as well as possible contra-indications of the use of bupropion and varenicline in people with SMD. In view of the low quality evidence, the GDG made conditional recommendations for tobacco cessation interventions in people with SMD.

3.2
WEIGHT MANAGEMENT

3.2.1

For people with SMD who are overweight or obese, are non-pharmacological and/or pharmacological interventions and/or pharmacological management strategies effective to support weight reduction?

Population:
People with SMD who are overweight or obese

Intervention:

- Non-pharmacological and/or pharmacological interventions and/or pharmacological management strategies:
  - Non-pharmacological interventions: e.g. cognitive-behavioural intervention strategies, lifestyle interventions (e.g. diet, exercise, physical activity / decreased sedentary behaviour, health education), family involvement in interventions
  - Pharmacological interventions: weight-loss medication (e.g. orlistat)
  - Pharmacological management strategies: e.g. switching antipsychotic medication

Comparison:
Care as usual and/or placebo

Outcomes:

- Critical
  - Change in weight
  - Mean BMI (kg/m^2) or change in BMI
- Important
  - Maintenance of weight change/attenuation/prevention of weight gain
  - Reduced sedentary behaviour
  - Frequency of adverse events/side-effects

3.2.2

For people with SMD who are at risk of becoming overweight or obese, are non-pharmacological interventions effective to support prevention of weight gain?

Population:
People with SMD who are at risk of becoming overweight or obese, e.g. people who have just started anti-psychotic medication

Intervention:
Non-pharmacological interventions, e.g. cognitive-behavioural intervention strategies, lifestyle interventions (e.g. diet, exercise, physical activity / decreased sedentary behaviour, health education), family involvement in interventions

Comparison:
Care as usual

Outcomes:

- Critical
  - Change in weight
  - Mean BMI (kg/m^2) or change in BMI
  - Maintenance of weight change
  - Attenuation/prevention of weight gain
- Important
  - Reduced sedentary behaviour
  - Frequency of adverse events/side-effects

BACKGROUND

Persons with SMD are 50% more likely to be obese than the general population; different studies have reported obesity rates of around 50% amongst women with SMD, and between around 30 to 40% for men with SMD (Dickerson *et al.*, 2006). People with SMD commonly have poor diets, and tend to consume more sugar and saturated fats than the general population. In addition, they are less likely to exercise, have a high prevalence of low physical activity, and spend over 12 hours on average in sedentary activities everyday (Janney, 2013). Also, increased appetite and metabolic effects of some psychotropic medicines can result in weight gain. Being overweight or obese may be

associated with higher rates of mortality and is related to other cardiovascular risk outcomes. Interventions in the general population have been described in the *Prevention and control of noncommunicable diseases: Guidelines for primary health care in low-resource settings (2012)* (http://www.who.int/nmh/publications/phc2012/en/).

RECOMMENDATIONS AND CONSIDERATIONS

RECOMMENDATION 1:

Behavioural lifestyle (healthy diet, physical activity) interventions should be considered in all people with severe mental disorders who are overweight or obese or at risk of becoming overweight or obese in accordance with *WHO's Package of Essential Noncommunicable Disease Interventions (WHO PEN) for primary care in low-resource settings (2010).* These interventions should be appropriate and tailored to the needs of this population.

(Strength of recommendation: Strong; Quality of evidence: Very low).

Package of Essential Noncommunicable Disease Interventions (WHO PEN) for primary care in low-resource settings (2010).

Prevention and control of noncommunicable diseases: Guidelines for primary health care in low-resource settings (2012) (http://www.who.int/nmh/publications/phc2012/en/)

- Advise overweight patients to reduce weight by following a balanced diet.
- Advise patients to give preference to low glycaemic-index foods (beans, lentils, oats and unsweetened fruit) as the source of carbohydrates in their diet.
- Advise patients to reduce sedentary behaviour and practice regular daily physical activity appropriate for their physical capabilities (e.g. walking).

RECOMMENDATION 2:

For people with severe mental disorders who are overweight or obese, and where lifestyle interventions and/or switching psychotropic medication do not appear successful, adjunctive metformin may be considered. This should be considered under close clinical supervision and monitoring.

(Strength of recommendation: Conditional; Quality of evidence: Low)

BEST PRACTICE STATEMENTS:

- For people with severe mental disorders who are overweight or obese or at risk of becoming overweight or obese, initiating a psychotropic medication with lower propensity for weight gain should be considered, taking into account clinical benefits and potential adverse effects.
- For people with severe mental disorders who are overweight or obese, switching to a psychotropic medication with a lower propensity for weight gain may be considered, taking into account clinical benefits and potential adverse effects.

Additional considerations

- Metformin is a commonly used anti-diabetic medication but it can be used for weight loss in people who are not diabetic. Metformin for people with SMD who are overweight or obese:
  - Should preferably be initiated in specialist settings, and should be closely monitored.
  - Should be tried in the short-term before being used in the long-term.
  - Availability may be an issue, i.e. metformin is not reliably available in all settings.
- Fluoxetine may increase the potency of metformin based on the drug-drug interaction searches (Annex 6). Monitor blood glucose control and adjust doses of metformin accordingly, especially when starting or stopping fluoxetine. Risperidone and clozapine are associated with hyperglycaemia and as such may decrease the efficacy of anti-diabetic medication including metformin. Monitor glycaemic control and adjust doses of anti-diabetic medications accordingly.

SUPPORTING EVIDENCE AND RATIONALE

Evidence was extracted from one systematic review with regards to lifestyle interventions for the prevention of weight gain amongst people with SMD who are at risk of becoming overweight/obese, though most of the studies in the review included participants who were already overweight (i.e. BMI over 25) on average. For this reason, the recommendations for the two PICO questions (3.2.1 and 3.2.2) were combined into one when formulating the recommendations.

For non-pharmacological interventions for weight management amongst people with SMD who were already overweight or obese, evidence was extracted from two systematic reviews for short-term lifestyle interventions (Gierisch *et al*., 2013; Naslund et al., 2017), and from one systematic review for long-term lifestyle interventions (Naslund *et al.*, 2017). With regards to anti-psychotic switching from olanzapine, evidence was extracted from one systematic review. Several systematic reviews have reported on the use of metformin for weight management amongst people with SMD who were already overweight or obese; evidence was considered from two systematic reviews when formulating the recommendations (Mizuno *et al*., 2014; de Silva *et al*., 2016).

The systematic reviews revealed very low to low quality evidence from randomized controlled trials for all of these interventions. With regards to all of the included lifestyle interventions, statistically significant effects were reported in favour of all of these. The most consistent evidence was for metformin, as – even though the quality of evidence was very low to low – the six systematic reviews from which evidence was extracted showed positive effects in terms of weight change when compared to placebo. The drug interaction review showed moderate interaction between metformin and some psychotropic medicines (fluoxetine, risperidone and clozapine) for which monitoring of blood glucose and dose adjustment may be needed. Other pharmacological interventions for which statistically significant weight change effects were found in the systematic reviews (Gierisch *et al*., 2013; Mizuno *et al*., 2014) were aripiprazole, reboxetine, sibutramine and topiramate, though the evidence base for these are only emerging and results need to be treated with caution. Sibutramine in particular has been withdrawn from use in several countries due to cardiac risks and so cannot be recommended. There is also some evidence in favour of switching from olanzapine to aripiprazole for the management of weight.

The GDG concluded that the behavioural lifestyle interventions recommended in the WHO guidelines for the general population should be followed in people with SMD since there is some evidence from the general population that advising people to give preference to low glycaemic index foods, follow a balanced diet and advice on exercise may have a beneficial effect on glycaemic control. Although the evidence in the general population is of low quality, these simple interventions are deemed as low-cost, feasible and with a negligible risk of adverse events. The GDG made a strong recommendation for non-pharmacological behavioural/lifestyle interventions, as they concluded that the benefits outweighed the harms including benefits of the intervention on other non-communicable disease outcomes. WHO general population guidelines (WHO PEN) also make a strong recommendation for these interventions in the general population. With regards to pharmacological interventions, the GDG made a strong recommendation for initiating a psychotropic medication with lower propensity for weight gain. The recommendation for switching antipsychotic medication was rated by the GDG as conditional since the quality of the evidence was low and switching antipsychotics because of weight gain should be offset against the risk of relapse of the mental disorder, as well as any potential side effects associated with the newly introduced medication.

3.3
SUBSTANCE USE DISORDERS

For people with SMD and substance (drug and/or alcohol) use disorder, are pharmacological and/or non-pharmacological interventions for substance use disorder effective to support reduction in substance use-related outcomes?

Population:
People with SMD and substance (drug and/or alcohol) use disorder

Intervention:
Pharmacological and/or non-pharmacological interventions for substance use disorders:

- Pharmacological interventions
- Non-pharmacological interventions:
  e.g. motivational interviewing and/or cognitive behaviour therapy (CBT), psychoeducation, brief assessment interview, dual-focus interventions

Comparison:
Care as usual / placebo or one treatment vs another

Outcomes:
- Critical
  - Level of consumption
  - Frequency of use
  - Abstinence
  - Relapse rates
- Important
  - Frequency of adverse events / side-effects

BACKGROUND

Comorbid substance use disorders are the most prevalent psychiatric conditions associated with SMD. The pooled prevalence for comorbid substance use disorders in SMD has been noted to range up to 42% (for alcohol use disorders), 69% (for cannabis use in schizophrenia), and just over 50% (for affective disorder amongst those on a methadone maintenance programme) (McLoughlin *et al*., 2014) (Di Florio, Craddock and van den Bree, 2014). The relationship between substance use disorders and SMD is likely bidirectional and their co-occurrence has been associated with a number of adverse outcomes, including: relapse of the mental disorder and longer hospital admissions, more positive symptoms in people with schizophrenia, and an increased risk of fatal and non-fatal overdoses and suicide.

There have been several Cochrane systematic reviews conducted on interventions for people with substance use disorder (in the general population), which have provided evidence on the effectiveness of the following interventions: Psychosocial interventions, such as combined motivational enhancement therapy (MET) and cognitive behaviour therapy (CBT) with abstinence-based incentives in cannabis use disorder (Gates *et al*., 2016); methadone in people with opioid dependence (Mattick *et al*., 2014). *WHO mhGAP Intervention Guide* provides recommendations for the management of substance use disorders. We have considered these pharmacological and/or non-pharmacological interventions for people with co-morbid SMD and substance use disorder.

RECOMMENDATIONS AND CONSIDERATIONS

RECOMMENDATION 1:

For people with severe mental disorders and comorbid substance use disorders (drug and/or alcohol) interventions should be considered in accordance with the WHO mhGAP guidelines.

(Strength of recommendation: Conditional; Quality of the evidence: Low).

RECOMMENDATION 2:

Non-pharmacological interventions (e.g. motivational interviewing) may be considered and tailored to the needs of people with severe mental disorders and substance use disorders.

(Strength of recommendation: Conditional; Quality of the evidence: Very low).

WHO mhGAP guidelines

(http://www.who.int/mental_health/mhgap/mhGAP_intervention_guide_02/en/)

The *mhGAP Intervention Guide* recommends the following:

- **Alcohol use disorders:**
  - Thiamine during alcohol use
  - Diazepam during alcohol detoxification to treat withdrawal symptoms
  - Naltrexone, acamprosate or disulfiram to prevent relapse after detoxification
  - Psychosocial interventions if available, e.g. cognitive behaviour therapy, motivational enhancement therapy, contingency management therapy, family counselling or therapy, problem-solving counselling or therapy; self-help groups
- **Drug use disorders:**
  - For opioid misuse: buprenorphine, methadone, clonidine, lofexidine, opioid agonist maintenance treatment (OAMT) for relapse prevention.
  - Psychosocial interventions, e.g. CBT, motivational enhancement therapy, contingency management therapy, family counselling or therapy, problem-solving counselling or therapy; self-help groups.

BEST PRACTICE STATEMENT:

- Prescribers should take into account the potential for drug-drug interactions between medicines used for treatment of substance use disorders and severe mental disorders.

Additional considerations

- Certain side effects (somnolence, hypersalivation, and constipation) may be more prevalent in people treated with clozapine, which should be a consideration when determining choice of pharmacotherapy.

- People with SMD who are injecting drug users may be at an increased risk of Hepatitis B and C through the sharing of contaminated instruments and/ or needles. The Centers for Disease Control and Prevention (CDC) in the USA has reported outbreaks of Hepatitis A in people who inject drugs, which may also be through the sharing of contaminated instruments and needles or through faeco-oral transmission. Therefore members of the GDG recommended that in people with SMD who also inject drugs, Hepatitis A and Hepatitis B vaccination, and Hepatitis B and Hepatitis C testing should be undertaken. This has also been recommended by the CDC, USA. (https://www.cdc.gov/hepatitis/populations/idu.htm).

SUPPORTING EVIDENCE AND RATIONALE

Evidence of pharmacological interventions for mental disorders comorbid with substance use disorders was extracted from two systematic reviews which focused on antipsychotic prescribing (Wilson and Bhattacharyya, 2016; Temmingh *et al.*, 2018) and one systematic review which focused on antidepressant prescribing in depression comorbid with alcohol use (Agabio *et al.*, 2018). Evidence on psychological interventions for these populations were extracted from two systematic reviews (Hunt *et al.*, 2014; Boniface, 2018).

Detailed reviews revealed very low to low quality evidence from randomized controlled trials, which did not support the superiority of any of the pharmacological interventions against each other. Potential side effects from pharmacological therapies were noted as moderate and will need to be considered when determining the choice of pharmacotherapy. Methadone and buprenorphine, medicines used for treatment of substance use disorders, have major interactions with commonly prescribed psychotropic medications including increased risk of for CNS depression (sedation, confusion, decreased respiratory drive), QT prolongation on ECG, and serotonergic effects (confusion, neuromuscular excitability, and dysautonomia) (Annex 6).

There was no evidence to support superiority of any of the psychosocial interventions against each other in populations with comorbid SMD and substance use disorder. None of the reviewed trials for psychosocial therapies have been conducted in LMIC settings. The absence of high quality evidence does not mean that these treatments do not work but that at present the evidence is of insufficient quality to support the use of one form of non-pharmacological or psychosocial intervention over another in these special populations. One reason for the lack of evidence may be that people with comorbidities are commonly excluded from research (Dennis *et al.*, 2015).

The resource requirements for offering interventions (both pharmacological and psychological) are currently unclear with only one study identified which estimated the cost of providing CBT plus motivational interviewing compared to care-as-usual in a well-resourced setting (USA).

There is good indirect evidence that certain interventions work for alcohol and substance use disorders in the general population, which have been detailed in the current mhGAP 2.0 guidelines, as well as in other guidelines such as those for Opioid Agonist Maintenance Treatment (OAMT) for relapse prevention. The GDG agreed that although the quality of evidence was very low for most psychological interventions in populations with co-morbid SMD and substance use disorders, the psychological interventions which are currently recommended in the MHGAP 2.0 guidelines for the general population (in particular- CBT plus motivational interviewing, motivational interviewing and contingency management) may also be effective in people with SMD . Furthermore, undesirable side effects from non-pharmacological treatments were noted to be trivial. Noting the risk of drug interactions between medicines used for treatment of opioid use disorders and SMD, the GDG agreed that the interactions are outweighed by the risk of other harms of untreated opioid use disorders in people with SMD and rather than withholding opioid replacement therapy, cautious medication management is advised.

Given the low quality of evidence and that all the evidence identified for the treatment of substance use disorders comorbid with SMD came from well-resourced/ high- income settings, the GDG made conditional recommendations.

3.4 CARDIOVASCULAR DISEASE AND CARDIOVASCULAR RISK

3.4.1

For people with SMD and pre-existing cardiovascular disease, what pharmacological and/or non-pharmacological interventions are effective to support reduction of cardiovascular disease outcomes?

Population:
People with SMD and pre-existing cardiovascular disease: e.g. coronary heart disease, prior heart failure or stroke, cardiomyopathy, congenital heart disease, peripheral vascular disease

Intervention:
Pharmacological and/or non-pharmacological interventions

Comparison:
One treatment versus another or care as usual / placebo

Outcomes:

- Critical
  - Major adverse cardiovascular event (MACE) - includes cardiovascular death, myocardial infarction, stroke, heart failure, hospitalization, amputation
- Important
  - Frequency of adverse events/side-effects

3.4.2

For people with SMD and cardiovascular risk factors (a. high blood pressure; b. high lipid levels), what pharmacological and/or non-pharmacological interventions are effective to support reduction of cardiovascular risk factors?

Population:
People with SMD and cardiovascular risk factors (a. high blood pressure; b. high lipid levels)

Intervention:
Pharmacological and/or non-pharmacological interventions:

- pharmacological interventions: a) medication to control high blood pressure; b) medications for high lipid levels
- non-pharmacological interventions

Comparison:
One treatment versus another or care as usual / placebo

Outcomes:

- Critical
  - Adequacy of control of CVD risk factors (a. blood pressure <130/80mmHg; b. cholesterol <200mg/dl)
  - Cardiovascular disease incidence
- Important
  - Frequency of adverse events/side-effects

BACKGROUND

Cardiovascular disease is considered as one of the main potentially avoidable contributors to excess mortality amongst people with SMD. Overall, people with SMD have an approximately 1.5 to 3 times higher risk of cardiovascular morbidity and mortality compared to the general population (Laursen, 2011). There is a complex interplay between several non-communicable diseases, such as diabetes, hypertension and cardiovascular disease, and the presence of SMD. People with SMD are more likely to engage in lifestyle behaviours that contribute to increased cardiovascular risk including tobacco use, harmful use of alcohol, unhealthy diets, and physical inactivity. The iatrogenic effects of medicines used to treat SMDs are linked with increased risk of cardiometabolic diseases. The use of antipsychotic medications has been associated with obesity, insulin resistance, diabetes, myocardial infarctions, atrial fibrillation, stroke, and death.

Pharmacological and non-pharmacological interventions for the general population have been described in the *Package of Essential Noncommunicable (PEN) Disease Interventions for Primary Health Care in Low-Resource Settings* (WHO, 2010).

RECOMMENDATIONS AND CONSIDERATIONS

RECOMMENDATION 1:

For people with severe mental disorders and pre-existing cardiovascular disease, or with cardiovascular risk factors (e.g. high blood pressure or high cholesterol), pharmacological and non-pharmacological interventions may be considered in accordance with the *WHO Package of Essential Noncommunicable Disease Interventions* (WHO PEN) for primary care in low-resource settings (2010) for lowering cardiovascular risk and management of cardiovascular disease.

(Strength of recommendation: Strong; Quality of evidence: High to moderate for different interventions).

Package of Essential Noncommunicable Disease Interventions (WHO PEN) for primary care in low-resource settings (2010).

http://www.who.int/cardiovascular_diseases/publications/pen2010/en/

- **Primary prevention of heart attacks and strokes:**
  - Tobacco cessation; regular physical activity 30 minutes a day; reduced intake of salt <5 g per day; fruits and vegetables at least 400g per day
  - Statins and antihypertensives for people with 10-year cardiovascular risk >30%
  - Antihypertensives for people with blood pressure ≥160/100
  - Anthypertensives for people with persistent blood pressure ≥140/90 and 10 year cardiovascular risk >20% unable to lower blood pressure through life style measures
- **Acute myocardial infarction: Aspirin and referral to next level of care**
- **Secondary prevention (post myocardial infarction):**
  - Tobacco cessation, healthy diet and regular physical activity.
  - Aspirin, antihypertensive (low dose thiazide, angiotensin-converting enzyme inhibitor), and statin
- **Secondary prevention (Rheumatic heart disease):**
  - Regular administration of antibiotics to prevent streptococcal pharyngitis and recurrent acute rheumatic fever

RECOMMENDATION 2:

For people with severe mental disorders and pre-existing cardiovascular disease, the following is recommended:

a) **Behavioural lifestyle (healthy diet, physical activity) interventions may be considered. These interventions should be appropriate and tailored to the needs of this population.**

(Strength of recommendation: Conditional; Quality of evidence: Very low).

b) **Collaborative care, i.e. a multi-professional approach to patient care with a structured management plan, scheduled patient follow-up, and enhanced inter-professional communication, may be considered for cardiovascular management.**

(Strength of recommendation: Conditional; Quality of evidence: Very low).

RECOMMENDATION 3:

For people with severe mental disorders and cardiovascular risk factors, behavioural lifestyle (healthy diet, physical activity) interventions may be considered. These interventions should be appropriate and tailored to the needs of this population.

(Strength of recommendation: Conditional; Quality of evidence: Very low).

BEST PRACTICE STATEMENTS:

For people with severe mental disorders and pre-existing cardiovascular disease:

- Initiating a psychotropic medication with lower propensity for cardiovascular risk is a strategy that should be considered, taking into account clinical benefits and potential adverse effects.
- Switching to a psychotropic medication with lower propensity for cardiovascular risk may be considered, taking into account clinical benefits and potential adverse effects.

For people with severe mental disorders and pre-existing cardiovascular disease or cardiovascular risk factors:

- Prescribers should be aware of potential interactions between prescribed medicines for cardiovascular disease and prescribed psychotropic medications, which may affect cardiovascular risk. Cardiovascular outcomes and risk factors should be monitored and dose adjustment of cardiovascular medicines may be required.

SUPPORTING EVIDENCE AND RATIONALE

For people with SMD and pre-existing cardiovascular disease, two systematic reviews were included that reported on anti-depressants as compared to care as usual (Maslej *et al.*, 2017; Nieuwsma *et al.*, 2017); one systematic review was included that reported on psychosocial interventions (Ski *et al.*, 2016); and one systematic review each for exercise therapy (Verschueren *et al.*, 2018) and collaborative care (Tully and Baumeister, 2015).

For people with SMD and cardiovascular risk (e.g. high blood pressure or cholesterol), regarding the use of pharmacological interventions, two systematic reviews were used to extract evidence on the use of metformin versus placebo (Mizuno *et al.*, 2014; de Silva *et al.*, 2016), and two on the use of aripiprazole versus placebo (Gierisch *et al*, 2013; Mizuno *et al*, 2014), in the management of either blood pressure or cholesterol, or the frequency of adverse effects. Two systematic reviews were included that reported on non-pharmacological interventions as compared to care as usual (Gierisch *et al*, 2013; Teasdale *et al*, 2017). None of these systematic reviews included cardiovascular disease incidence as an outcome which is one of the critical outcomes for this PICO question. All of the systematic reviews and meta-analyses for comorbid cardiovascular disease focused on interventions for people with depression. No reviews assessed interventions in populations with other SMD (e.g. schizophrenia, bipolar disorder) with comorbid cardiovascular disease. The evidence and recommendations are therefore indirect for populations with SMD and comorbid cardiovascular disease.

No sufficiently high-quality systematic reviews could be identified that reported on either pharmacological or non-pharmacological interventions compared to another treatment, either for SMD and pre-existing cardiovascular disease or cardiovascular risk.

The systematic reviews revealed either very low or low quality evidence from randomized controlled trials for all of these interventions; the only exception to this was for psychosocial interventions for people with SMD and pre-existing cardiovascular disease, for which some of the evidence was graded as moderate quality. The only included intervention for which statistically significant effects were reported for people with SMD and pre-existing cardiovascular disease was collaborative care, which may show a relative and absolute reduction in major adverse cardiac events in the short to medium-term (less than 12 months), though it is less clear whether this is the case in the longer-term (over 12 months).

Major drug-drug interactions were found between several psychotropic medications and commonly prescribed medications for cardiac conditions, hypertension and cholesterol control. Some examples of these are: the risk of hypotension or beta-blocker toxicity (including hypotension, bradycardia, and heart block/prolonged PR interval) with beta blockers and the risk of hypotension with diuretics (Annex 6).

Given the evidence was limited for people with SMD, the GDG used evidence from general populations and thought it to be applicable because they would benefit people with SMD too. However, the GDG agreed that it is important to exercise caution in the initiation of psychotropic medication due to the heightened risk of cardiovascular disease and potential drug interactions. There is currently insufficient evidence for behvioural lifestyle interventions for people with SMD and cardiovascular disease and risk, conditional recommendations have been made for these interventions as the GDG agreed that there the benefits outweighed the risks including benefits of the intervention on other non-communicable disease outcomes.

3.5 DIABETES MELLITUS

For people with SMD and diabetes mellitus, what pharmacological and/or non-pharmacological interventions are effective to improve glycaemic control?

Population:
People with SMD and diabetes mellitus

Intervention:
- Pharmacological interventions: e.g. medication to treat diabetes
- Non-pharmacological interventions: e.g. behavioural lifestyle interventions, cognitive behaviour therapy

Comparison:
One treatment versus another or care as usual

Outcomes:
- Critical
  - Fasting blood glucose <120mg/dl; post-prandial blood glucose<160mg/dl
  - Glycosylated haemoglobin A1c (HbA1c<7 for people below 60 years and 7-8 for people above 60 years with other risk factors)
  - Diabetes complications – Major Atherosclerotic Cardiovascular Events (MACE), chronic kidney disease, diabetic retinopathy, diabetic neuropathy, hospitalization for infection
- Important
  - Frequency of adverse events/side-effects

BACKGROUND

There is high co-morbidity between SMD and diabetes mellitus. People with SMD are at an increased risk of diabetes (around double for schizophrenia and bipolar disorder, and 1.5 times the risk for depression), and people with diabetes are at a heightened risk of SMD (around double for depression), with a higher risk in low- and middle-income countries(Vancampfort et al., 2016). However, this often goes undetected, and people with comorbid SMD and diabetes have an increased risk of mortality. There is an association with diabetes with some anti-psychotics, anti-depressants and lithium, as well as with health-related behaviours (such as physical activity and diet), other environmental factors, and gender (elevated risk in women).

This section covers evidence regarding pharmacological and/or non-pharmacological interventions for people with SMD and diabetes mellitus. The inclusion of interventions was guided by the research evidence available for people with diabetes and SMD.

RECOMMENDATIONS AND CONSIDERATIONS

RECOMMENDATION 1:

For people with severe mental disorders and diabetes mellitus, interventions in accordance with the *WHO Package of Essential Non-communicable (PEN) Disease Interventions for primary care in low-resource settings* should be considered for diabetes management

(Strength of recommendation: Strong; Quality of evidence: Low).

Package of Essential Noncommunicable Disease Interventions (WHO PEN) for primary care in low-resource settings (2010)

http://apps.who.int/iris/bitstream/handle/10665/133525/9789241506557_eng.pdf;jsessionid=C8B92D24C7F27E9E3BEBC2957FB8CCE8?sequence=1

- **For Type 1 diabetes:**
  - Daily insulin injections
- **For Type 2 diabetes:**
  - Anti-diabetic agents for type 2 diabetes, if glycaemic targets are not achieved with modification of diet, maintenance of a healthy body weight and regular physical activity
  - Metformin as initial drug in overweight patients and non-overweight
  - Other classes of anti-diabetic agents, added to metformin if glycaemic targets are not met
  - Reduction of cardiovascular risk for those with diabetes and 10-year cardiovascular risk >20% with aspirin, angiotensin converting enzyme inhibitor and statins

WHO NCD 2012: Prevention and control of noncommunicable diseases: Guidelines for primary health care in low-resource settings

(http://www.who.int/nmh/publications/phc2012/en/):

- **Diagnosing diabetes:** Laboratory services. If not available, point of care devices may be used
- **Glycaemic control:** Diet and physical activity as first-line treatment, Metformin as first-line oral hypoglycaemic agent where diet is not sufficient, sulfonylureas for those patients where metformin is not effective/patient has contraindications
- **Reducing the risk of cardiovascular disease and diabetic nephropathy:** Statins for all people with Type-2 diabetes over 40 years of age, antihypertensive agents to reduce blood pressure, choice of antihypertensive agent
- **Prevention of lower limb amputations:** Educate patients and health care workers
- **Prevention of blindness:** Screening for diabetic retinopathy
- **Severe hypoglycaemia, hypoglycaemic emergencies**: Intravenous hypertonic glucose treatment or glucose (dextrose) for unconscious patients, referral to hospital and drip in emergencies

RECOMMENDATION 2:

Behavioural lifestyle interventions should be considered for all people with severe mental disorders and diabetes mellitus. These interventions should be appropriate and tailored to the needs of this population.

(Strength of recommendation: Strong; Quality of evidence: Very low).

RECOMMENDATION 3:

In people with depression and comorbid diabetes mellitus, cognitive behaviour therapy for treatment of depression may be considered.

(Strength of recommendation: Conditional; Quality of evidence: Very low).

BEST PRACTICE STATEMENTS:

For people with severe mental disorders and diabetes mellitus:

- Initiating an anti-psychotic medication with lower propensity for producing hyperglycaemia should be considered, taking into account clinical benefits and potential adverse effects.
- Switching to an anti-psychotic medication with lower propensity for producing hyperglycaemia is a strategy that may be considered, taking into account clinical benefits and potential adverse effects.
- Prescribers should be aware of potential interactions between prescribed medicines for diabetes and prescribed psychotropic medicines, which may affect glycaemic control. Glycaemic control should be monitored and dose adjustment of medicines may be required.

SUPPORTING EVIDENCE AND RATIONALE

With regards to pharmacological interventions for people with SMD and diabetes, one (the same) systematic review was used to extract evidence for diabetes medication, weight loss medications, anti-psychotic switching, and weight loss and diabetes medications combined.

The systematic reviews revealed very low quality evidence from randomized controlled trials for all of these interventions. There was some evidence to suggest anti-psychotic switching had beneficial effects. The drug-drug interaction review showed moderate interactions between some psychotropic medicines and anti-diabetic medicines (increased or decreased potency of the anti-diabetic medicine) that requires blood glucose monitoring and dose adjustment of anti-diabetic medicines.

With regards to non-pharmacological interventions, evidence from one systematic review each was considered for behavioural interventions (Taylor *et al.*, 2017) and cognitive behaviour therapy (Li *et al.*, 2017), and one systematic review for self-management interventions (McBain *et al.*, 2016). There was some evidence that cognitive behaviour therapy for treatment of depression shows positive effects on blood glucose amongst people with diabetes and comorbid depression (probably by eliminating the negative effects of depression on diabetes). There is insufficient evidence available for the management of diabetes amongst people with SMD for all other reviewed interventions.

Since all of the evidence was rated as very low in quality, and there was insufficient evidence available for most of the reviewed interventions, the GDG concluded that the WHO guidelines for the general population in low-resource settings should be followed as a first step as the underlying pathophysiological mechanisms would be similar in people with SMD. Nevertheless, the GDG made additional best practice statements for the initiation of psychotropic medication and potential drug-drug interactions, to counter the risks of taking these medications. A strong recommendation has also been made for behavioural lifestyle interventions despite very low quality evidence as the GDG agreed that the benefits outweighed the harms and as there is a strong recommendation for this by WHO for the general population (WHO PEN). The GDG also concluded that there are benefits of the intervention on other noncommunicable disease outcomes. The GDG made a conditional recommendation for cognitive behaviour therapy because of very low quality evidence and the possible lack of generalizability to all people with SMD.

3.6 HIV/AIDS

For people with SMD and HIV/AIDS, what pharmacological (i.e. antiretroviral drugs, psychopharmacology) and nonpharmacological interventions are effective to support reduction in HIV-related outcomes?

Population:
People with SMD and HIV/AIDS

Intervention:
- Pharmacological interventions (e.g. antiretroviral drugs, psychopharmacology)
- Nonpharmacological interventions

Comparison:
One treatment versus another or care as usual

Outcomes:
- Critical
  – HIV-related outcomes
- Important
  – Frequency of adverse events/side-effects

BACKGROUND

The association between mental health disorders and HIV/AIDS is complex and bi-directional - they frequently co-occur: mental disorders can be precursors to HIV/AIDS, consequences of HIV infection, or the result of interactive effects. They also have similar consequences in terms of their public health, social, and economic impacts.

International evidence has found that populations with SMD have higher rates of HIV infection. Among persons with SMD, the median prevalence of HIV in the US is 1.8 % (range: 0.1%-5.0%) with a high rate among inpatient populations (3.8%), whereas the overall US adult population estimated prevalence of HIV is 0.5% (Janssen *et al.*, 2015). HIV rates may be even higher in certain vulnerable populations, such as those who have SMD and are also homeless(Susser, Valencia and Conover, 1993). People with SMD and HIV experience a complex set of medical, psychological and social complications that need to be tackled through integrated care. The interventions included pharmacological interventions for SMD and HIV as well as non-pharmacological interventions such as psychosocial support.

RECOMMENDATIONS AND CONSIDERATIONS

RECOMMENDATION 1:

For people with severe mental disorders and HIV/ AIDS, antiretroviral drugs should be considered in accordance with the WHO Updated recommendations on first-line and second-line antiretroviral regimens.

(Strength of the recommendation: Strong; Quality of the evidence: Moderate)

Updated recommendations on first-line and second-line antiretroviral regimens and post-exposure prophylaxis and recommendations on early infant diagnosis of HIV: interim guidelines. Supplement to the 2016 consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection. Geneva: World Health Organization; 2018 (WHO/ CDS/HIV/18.45). Licence: CC BY-NC-SA 3.0 IGO.

http://www.who.int/hiv/pub/guidelines/ARV2018update/en/

RECOMMENDATIONS: FIRST-LINE ARV DRUG REGIMENS

A DTG based regimen is recommended as a preferred first-line regimen for people living with HIV initiating ART (conditional recommendation)

- Adults and adolescents (moderate-certainty evidence)
- Women and adolescent girls of childbearing potential (very-low-certainty evidence)
  Note of caution on using DTG during the periconception period and for women and adolescent girls of childbearing potential*
- Exposure to DTG at the time of conception may be associated with neural tube defects among infants.
- DTG appears to be safe when started later in pregnancy: after the period of risk of neural tube defects, up to eight weeks after conception.
- Adolescent girls and women of childbearing potential who do not currently want to become pregnant can receive DTG together with consistent and reliable contraception; based on limited data, hormonal contraception and DTG have no reported or expected drug–drug interactions.
- An EFV-based regimen is a safe and effective first-line regimen recommended for use by the WHO 2016 ARV drug guidelines and can be used among women of childbearing potential during the period of potential risk for developing neural tube defects (at conception and up to eight weeks after conception).

Further guidance on the treatment and care of people living with HIV can be found in *"Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach – 2nd edition 2016."* http://www.who.int/hiv/pub/arv/arv-2016/en

[List of abbreviations: DTG: dolutegravir; EFV efavirenz]

* an ongoing observational study in Botswana recently identified a signal of potential safety risk for developing neural tube defects among infants born to women who were taking DTG at conception. WHO is taking this potential safety issue seriously and is working closely with all relevant stakeholders to further investigate these preliminary findings. WHO will update these guidelines and provide additional information as it becomes available

RECOMMENDATION 2:

Additional psychosocial support for treatment adherence should be provided to people with HIV and severe mental disorders in accordance with the WHO consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection.

(Strength of the recommendation: Strong; Quality of the evidence: Moderate)

Adherence support interventions extracted from WHO Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach – 2nd ed. 2016

http://apps.who.int/iris/bitstream/handle/10665/208825/9789241549684_eng.pdf?sequence=1

RECOMMENDATION: Adherence support interventions should be provided to people on ART (strong recommendation, moderate-quality evidence).

The following interventions have demonstrated benefit in improving adherence and viral suppression:

- peer counsellors (moderate-quality evidence)
- mobile phone text messages (moderate-quality evidence)
- reminder devices (moderate-quality evidence)
- cognitive-behavioural therapy (moderate-quality evidence)
- behavioural skills training and medication adherence training (moderate-quality evidence)
- fixed-dose combinations and once-daily regimens (moderate-quality evidence).

Considerations in specific populations: People with HIV with uncontrolled depressive symptoms are more likely to have poor adherence to ART. Adherence is complicated by mental health comorbidity that results in forgetfulness, poor organization and poor comprehension of treatment plans. Counselling for HIV and depression and appropriate medical therapies for people with mental disorders can help to improve adherence. WHO recommends that assessment and management of depression should be included in care services for all people living with HIV.

BEST PRACTICE STATEMENT:

For people with severe mental disorders and HIV/ AIDS prescribers should take into account the potential for drug-drug interactions between antiretroviral drugs and psychotropic medicines.

SUPPORTING EVIDENCE AND RATIONALE

There is limited RCT evidence for pharmacological treatment in people with SMD and HIV/AIDS. One systematic review that was included in the evidence profile assessed the efficacy of antidepressant therapy for treatment of depression in people with HIV/AIDS (Eshun-Wilson, 2018). The evidence was of very low quality and the results inconclusive. The drug interaction review reveals multiple interactions between efavirenz and psychotropic medicines, specifically involving the risk of QT interval prolongation, CNS depression and /or enzyme induction (Annex 6). No reviews were identified for non-pharmacological treatments including adherence management specifically in people with SMD and comorbid HIV/ AIDS.

These recommendations are based on indirect evidence of HIV treatment in the general population that are provided in existing WHO guidelines that strongly recommend ARV and adherence management to support ARV adherence in people with HIV/AIDS with or without SMD. The GDG concluded that the balance between desirable and undesirable effects favor the intervention leading to strong recommendations while noting the need to consider drug interactions. They also concluded that there was no important uncertainty about or variability in how much people value the main outcomes and that the interventions would increase health equity. The GDG agreed that people with SMD would need additional support for adherence as the presence of SMD and its associated symptoms can have a detrimental impact on adherence to ARV and progression of AIDS.

3.7
OTHER INFECTIOUS DISEASES (TUBERCULOSIS, HEPATITIS B/C)

For people with SMD and infectious diseases (Tuberculosis, Hepatitis B/C), what pharmacological and nonpharmacological (social, psychological) interventions are effective for treatment of infectious diseases (i.e. tuberculosis, hepatitis B, hepatitis C)?

Population:
People with SMD and infectious diseases (Tuberculosis, Hepatitis B/C)

Intervention:

- Pharmacological interventions for infectious diseases
- Nonpharmacological (social, psychological) interventions for infectious diseases

Comparison:
One treatment versus another or care as usual

Outcomes:

- Critical
  – Infectious disease-related outcomes
- Important
  – Frequency of adverse events/side-effects

BACKGROUND

People with SMD are at greater risk than the general population for exposure to infectious diseases, including tuberculosis (TB) and chronic hepatitis(Rosenberg *et al.*, 2010). Infectious diseases appear to contribute to an increased risk of death in persons with SMD, with a 4- to 8-fold risk of death due to infection compared to the general population.

Tuberculosis and SMD share common risk factors including homelessness, HIV positive serology, alcohol/substance abuse and migrant status leading to frequent co-morbidity. There are widespread discriminatory attitudes and behaviours towards patients with TB and SMD in the community which affects health-related quality of life. In people with SMD and TB, there may be a negative impact on health behaviours such as medication adherence leading to greater morbidity, mortality, amplification of drug-resistance, transmission and all the associated social costs of these outcomes (Alene *et al.*, 2018).

The WHO End TB strategy calls to provide TB care through an integrated approach in collaboration with other public health programmes including mental health services such as tailoring TB care delivery models to the specific needs of populations with mental health problems.

There is also a high prevalence of hepatitis B and C in people with SMD. There is evidence that hepatitis C infection itself may be directly associated with psychiatric symptoms, independent of pre-existing psychiatric disorders. Stigmatization and the fact that people have to cope with a chronic infectious disorder increase the risk of depression. As is seen with TB, mental health problems during antiviral treatment have a strong impact on quality of life, may reduce treatment compliance and are risk factors for treatment failure.

For people with SMD and TB or hepatitis B/C, pharmacological and non-pharmacological interventions need to be considered as in the general population.

RECOMMENDATIONS AND CONSIDERATIONS

RECOMMENDATION 1:

For people with severe mental disorders and TB, pharmacological management should be considered in accordance with the *WHO guidelines for the treatment of drug-susceptible tuberculosis and patient care*, and the *WHO treatment guidelines for drug-resistant tuberculosis*.

(Strength of the recommendation: strong; Quality of the evidence: Low).

WHO guidelines for the treatment of drug-susceptible tuberculosis and patient care

(http://apps.who.int/iris/bitstream/handle/10665/255052/9789241550000-eng.pdf?sequence=1)

In patients with drug-susceptible pulmonary TB, the 6-month rifampicin-based regimen 2HRZE/4HR and daily dosing is the recommended regimen and dosing frequency.

WHO treatment guidelines for drug-resistant tuberculosis

(http://apps.who.int/iris/bitstream/handle/10665/250125/9789241549639-eng.pdf?sequence=1).

Note: The guidelines are currently being updated and the recommendations will be replaced with the revised ones as soon as they are available.

1) Shorter MDR-TB regimen

In patients with RR-TB or MDR-TB who were not previously treated with second-line drugs and in whom resistance to fluoroquinolones and second-line injectable agents was excluded or is considered highly unlikely, a shorter MDR-TB regimen of 9–12 months may be used instead of the longer regimens (conditional recommendation, very low certainty in the evidence).

2) Longer MDR-TB regimens

2a) In patients with RR-TB or MDR-TB, a regimen with at least five effective TB medicines during the intensive phase is recommended, including pyrazinamide and four core second-line TB medicines – one chosen from Group A, one from Group B, and at least two from Group C2 (conditional recommendation, very low certainty in the evidence). If the minimum number of effective TB medicines cannot be composed as given above, an agent from Group D2 and other agents from Group D3 may be added to bring the total to five.

2b) In patients with RR-TB or MDR-TB, it is recommended that the regimen be further strengthened with high-dose isoniazid and/or ethambutol (conditional recommendation, very low certainty in the evidence).

(Group A=levofloxacin, moxifloxacin, gatifloxacin; Group B=amikacin, capreomycin, kanamycin, (streptomycin); Group C= ethionamide (or prothionamide), cycloserine (or terizidone), linezolid, clofazimine).(Group D2=bedaquiline, delamanid; Group D3=p-aminosalicylic acid, imipenem–cilastatin, meropenem, amoxicillin clavulanate, (thioacetazone)).

RECOMMENDATION 2:

For people with severe mental disorders and TB, non-pharmacological (social, psychological) management should be considered in accordance with the WHO guidelines for the treatment of drug-susceptible tuberculosis and patient care, and the WHO treatment guidelines for drug-resistant tuberculosis.

(Strength of the recommendation: strong; Quality of the evidence: Low).

Cross-cutting interventions for drug-susceptible TB and drug-resistant TB: effectiveness of patient care and support interventions

(http://apps.who.int/iris/bitstream/handle/10665/255052/9789241550000-eng.pdf?sequence=1)

RECOMMENDATIONS:

Health education and counselling on the disease and treatment adherence should be provided to patients on TB treatment. (Strong recommendation, moderate certainty in the evidence)

A package of treatment adherence interventions may be offered to patients on TB treatment in conjunction with the selection of a suitable treatment administration option. (Conditional recommendation, low certainty in the evidence)

One or more of the following treatment adherence interventions (complementary and not mutually exclusive) may be offered to patients on TB treatment or to health-care providers: a) tracers and/or digital medication monitor (Conditional recommendation, very low certainty in the evidence) b) material support to patient (Conditional recommendation, moderate certainty in the evidence) c) psychological support to patient (Conditional recommendation, low certainty in the evidence) d) staff education (Conditional recommendation, low certainty in the evidence).

[The GDG suggests that psychological support* should be provided to patients with TB (conditional recommendation, low certainty of evidence). *Psychological support includes counselling sessions and peer-group support.]

Psychological support was varied and could include self-help groups, alcohol cessation counselling and TB clubs. Patients who had access to psychological support had higher rates of treatment completion and cure, as well as lower rates of treatment failure and loss to follow-up. When considering this data, it should also be noted that psychological support types are very broad and may not be adequately represented in this review. To maximize health equity, psychological support should be targeted at the most marginalized populations.

RECOMMENDATION 3:

For people with severe mental disorders and hepatitis B, treatment should be considered in accordance with the WHO guidelines for the prevention, care and treatment of persons with chronic hepatitis B infection.

(Strength of the recommendation: strong; Quality of the evidence: Low)

Guidelines for the prevention, care and treatment of persons with chronic hepatitis B infection. March 2015

http://apps.who.int/iris/bitstream/handle/10665/154590/9789241549059_eng.pdf?sequence=1

In all adults, adolescents and children aged 12 years or older in whom antiviral therapy is indicated, the nucleos(t)ide analogues (NAs) which have a high barrier to drug resistance (tenofovir or entecavir) are recommended. Entecavir is recommended in children aged 2–11 years. *(Strong recommendation, moderate quality of evidence)*

RECOMMENDATION 4:

For people with severe mental disorders and hepatitis C, treatment should be considered in accordance with the WHO guidelines for the screening care and treatment of persons with chronic hepatitis C infection.

(Strength of the recommendation: strong; Quality of the evidence: Low)

Guidelines for the screening care and treatment of persons with chronic hepatitis C infection. Updated version, April 2016

http://www.who.int/hepatitis/publications/hepatitis-c-guidelines-2016/en/

Treatment with direct-acting antiviral agents: it is recommended that direct-acting antivirals (DAA) regimens be used for the treatment of persons with hepatitis C infection rather than regimens with pegylated interferon and ribavirin. *(Strong recommendation, moderate quality of evidence)*

BEST PRACTICE STATEMENT:

For people with severe mental disorders and TB, Hepatitis B/C prescribers should take into account the potential for drug-drug interactions between TB medicines, medicines for hepatitis B and C with psychotropic medicines.

Additional considerations

People with SMD may be at an increased risk of Hepatitis B and C for example due to injection drug use. The CDC in the USA has reported outbreaks of Hepatitis A in people who inject drugs, which may also be through the sharing of contaminated instruments and needles or through faeco-oral transmission. Therefore members of the GDG recommended that in people with SMD who also inject drugs, Hepatitis A and Hepatitis B vaccination, and Hepatitis B and Hepatitis C testing should be undertaken. This has also been recommended by the CDC, USA (https://www.cdc.gov/hepatitis/populations/idu.htm).

SUPPORTING EVIDENCE AND RATIONALE

No reviews were identified for interventions in people with SMD and comorbid TB, Hepatitis B/C. A recent systematic review reported that programmes that included educational, psychological, and/or material support were associated with better TB outcomes, and can now be considered best practice(Alipanah *et al*., 2018). Some trial evidence shows effectiveness of treatment of pulmonary TB in people with SMD (Mishin *et al* 2008) and of a brief intervention to deliver best practice services for infectious diseases to people with mental disorders in increasing participation and acceptance of core services, including testing for hepatitis B/C; immunization for hepatitis A and B; increased hepatitis knowledge reduction of substance use (Rosenberg *et al*., 2010).

The drug-drug interaction review showed that major interactions exist between medicines used for TB, hepatitis B/C and psychotropic medicines (Annex 6). These require close clinical monitoring and dose adjustments and in some cases use of alternate psychotropic medicines with less potential for interaction.

These recommendations are based on indirect evidence of TB/Hepatitis treatment in the general population that are provided in existing WHO guidelines as the GDG concluded that the same pathophysiological mechanisms for these conditions would apply to people with SMD. The GDG provided strong recommendations as they agreed that the benefits of the interventions outweighed the harms while noting the need to consider drug interactions. The GDG also agreed that there was no important uncertainty about or variability in how much people value the main outcomes and that the interventions would increase health equity. The GDG agreed that people with SMD would need additional support for adherence to TB treatments and provided a strong recommendation for this intervention drawing from existing general population guidelines.

4. Implementation considerations

The recommendations in these guidelines must be implemented using a person-centred and integrated approach to address factors associated with excess mortality in persons with SMD. This integration is needed at four levels – screening and early detection of physical health conditions, counselling for behavioural risk factors, assessment and management of cardiovascular disease risk and management of established physical and mental health conditions.

We propose a multilevel intervention framework that will be useful for designing, implementing and evaluating interventions and programmes to reduce excess mortality in persons with SMD (Liu et al., 2017). The first level is individual-focused interventions. The second and third levels of the framework consist of strategies focussed on the health systems and socio-environmental context, respectively, which provide the enabling environment for implementation of the recommendations.

The ***individual-focused interventions*** i.e. strategies delivered to individuals with SMD to target their mental health condition, physical health and lifestyle behaviours should be guided by the recommendations proposed in these guidelines.

Health screening facilitates early detection and treatment for many of these conditions, though rates of screening in people with SMD appear to be reduced compared with the general population. A UK survey(Patel *et al.*, 2014) found that only 33% of people with schizophrenia had received adequate cardiovascular disease screening in the previous 12 months. Effective interventions for increasing access to, or uptake of, screening for a range of conditions in the general population (Camilloni *et al.,* 2013) exist. A recent review identified interventions to increase both access to and uptake of physical health screening in people with SMD amongst which are staff and stakeholder involvement in screening, staff flexibility when taking physical measurements (e.g. using adapted equipment) and strong links with primary care (Lamontagne-Godwin *et al.*, 2018).

Psychosocial interventions that promote adherence in people with SMD are particularly important when addressing physical health conditions. This can also take the form of generic advice and psychoeducation at the time of diagnosis of the SMD.

Adherence to medication guidelines − such as the American Schizophrenia Patient Outcomes Research Team (PORT) Treatment Recommendations (Kreyenbuhl *et al.*, 2010) − appear to have an effect on reducing mortality in schizophrenia. These, along with other specific recommendations for psychosocial treatments as described in these guidelines, are important considerations when developing intervention plans for people with SMD. The full participation of persons with SMD in their treatment and recovery plans is a very important factor in improving health outcomes (Vahdat *et al.*, 2014).

The next level in the framework encompasses strategies within ***health systems*** targeting health care providers and service delivery components. These will vary across different settings depending upon many parameters, such as the number of specialists versus primary care providers, the different distribution of health risk factors, the presence or absence of universal health care, and the availability of health technologies and medications. Strengthening of the six building blocks of the health systems – service delivery; health workforce; information; medical products, vaccines and technologies; financing; and leadership and governance (stewardship) – would improve outcomes for persons with SMD.

Care coordination, collaborative care or integrated care programmes that include support to better equip health systems, usually through the provision of additional supportive members who can serve as a liaison between mental health and physical health care systems or through linking of delivery of physical and mental health services are particularly important. Mental health practitioners need to be better at physical health skills, as well as physical health clinicians/ systems being better at addressing needs of people with SMD.

In countries with limited resources, evidence suggests that mental health care can be delivered effectively in primary health-care settings, through community-based programmes and task-shifting approaches. Non-specialist health professionals, lay workers, affected individuals, and caregivers with brief training and appropriate supervision by mental health specialists are able to detect, diagnose, treat, and monitor individuals with mental disorders and reduce caregiver burden. Physical health in people with SMD should also be considered in community-based programmes and task-shifting approaches (Kakuma *et al.*, 2011).

The broadest level of the framework incorporates ***socio-environmental factors*** and the social determinants of health. This part of the model acknowledges the range of potential strategies originating from the community to address contributors to premature mortality such as peer and family support programmes and stigma reduction programmes. At a wider level, public health policies providing mental health parity are essential to improve lives of those with SMD. A twin-track approach is likely to work best with improved public health for all, recognising that the broader social determinants like poverty affect certain groups more, and, targeted interventions for at-risk groups. Strategies at the policy level that affect screening or management of HIV, TB or tobacco consumption are especially relevant to those with SMD and may have even greater effects on the health and well-being of this high-risk population.

The recommendations contained in these guidelines should be adapted into a locally appropriate document that can meet the needs of each country and its health services. WHO headquarters will work closely with the regional and country offices, as well as implementing partners, to ensure communication and country-specific adaptations of the guidelines, through regional and national meetings.

As countries consider how to implement these guidelines, the budgetary and human resource requirements, and other health systems implications should be analysed to identify which inputs and systems are currently available, and which areas require additional investment, including training of health workers; supply of medicines; and adaptations of health information systems to collect data on service utilization.

To support country implementation, WHO will produce a series of subsidiary tools that will address clinical and service delivery aspects of the implementation of the recommendations included in these guidelines.

5. Publication, dissemination, and evaluation

5.1 PUBLICATION AND DISSEMINATION

The guidelines are disseminated as a print publication and electronically on a dedicated internet space on the WHO website (http://www.who.int/mental_health/evidence/guidelines_physical_health_and_severe_mental_disorders/en/index.html).

WHO publications, training and clinical management manuals will be revised to reflect the updated recommendations. A range of subsidiary products will be developed to support the implementation including job aids and policy briefs.

The guidelines and products are developed in English, and will be translated into other WHO official languages for wider dissemination and in collaboration with WHO Regional Offices.

Dissemination will be supported by publication of selected systematic reviews and evidence in peer review journals, and presentations and workshops at key conferences and events.

5.2 MONITORING AND EVALUATION

Implementation of the recommendations will be monitored at the health facility level. Facility data will be collected through surveys or routine health information systems. Special studies can be considered where routine monitoring is not feasible or appropriate.

WHO will continue to solicit and collect regular feedback through process indicators by Ministries of Health regarding implementation activities in order to evaluate the impact and usefulness of this guideline. This feedback will also identify areas where improvement is warranted.

5.3 IMPLICATIONS FOR FURTHER RESEARCH

While evidence for mental health treatments is strong, the evidence for effectiveness of interventions to prevent and treat physical conditions in those with SMD is limited. Interventions developed for the general population geared at non-communicable diseases, infectious diseases or other health problems are likely as effective for persons with SMD but given the special needs of this population, interventions for SMD require tailoring. However, more research is needed on the degree of tailoring required. For this, it is essential to include people with SMD in research studies to a much greater extent than is being currently done.

For current evidence-based interventions, research is needed on optimal length and dose needed to positively affect health, which will also be important for resource allocation. Multimodal approaches, which can include behavioural plus pharmacological interventions and include components such as peer support or technology are promising, but have yet to be studied systematically to clarify whether or which multicomponent programs are effective, and which components of the intervention are most beneficial. Many people with SMD have multiple cardiovascular and other risk behaviours which may be modifiable, and future research should test interventions addressing multiple risk factors, as well as those which are directly linked to mortality.

Cost-effectiveness models of different approaches in people with SMD are important, especially in low resource settings, as we aim to achieve universal health coverage and to address the physical health needs of this vulnerable population.

Research is needed to identify and manage barriers to and facilitators of implementing evidence-based guidance and policy recommendations. We need to understand how to deliver evidence-based interventions successfully in the real world, taking into account training and workforce issues and often-limited resources in local community settings. We need to understand to what extent interventions and programmes could or should be disseminated across countries.

Another important area of research will be to assess the effects of health system and policy interventions on excess mortality in SMD. We need to understand why those with SMD have not benefitted from trends in the general population towards reduced mortality in some diseases and smoking cessation. Researchers should take advantage of natural experiments and also design studies in health systems and at the population level to evaluate the impact of these programmes.

Finally, to gain a better understanding of the different perspectives involved, qualitative research is needed to understand the experiences of users, providers, family members, as well as professionals' receptivity to education and training.

5.4 FUTURE REVIEW AND UPDATE

These guidelines will be reviewed in three to five years, unless an earlier review and update is warranted by breakthrough research. New evidence in these areas is regularly monitored by the WHO Secretariat, in consultation with GDG members and technical experts identified for the evidence review process, WHO collaborating centres, and academic institutions.

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Annex 1. Guideline Development Group (GDG) members

	Name	Gender	WHO Region	Affiliation	Area of expertise
1.	**Abdullah Al Khathami**	M	**EMR**	Ministry of Health, Saudi Arabia	Family and community medicine, medical education, program management
2.	**Corrado Barbui**	M	**EUR**	University of Verona, Italy	Mental health research and training, public health, health systems strengthening
3.	**Jackie Curtis**	F	**WPR**	University of New South Wales, Australia	Psychiatry, early psychosis, comorbidity
4.	**Gail L. Daumit**	F	**AMR**	Johns Hopkins Medical Institutions, Division of General Internal Medicine, Welch Center for Prevention, Epidemiology and Clinical Research Baltimore, USA	Psychiatry, Epidemiology, Health Policy and Management and Mental Health
5.	**Chris Dowrick**	M	**EUR**	University of Liverpool, Institute of Psychology, Health and Society	Medically unexplained somatic complaints, mental health in primary care, guideline development (NICE) for depression
6.	**Benjamin Druss**	M	**AMR**	Center for Behavioural Health Policy Studies, Rollins School of Public Health, 1518 Clifton Rd, Atlanta, USA	Health policy, health outcomes and mental health
7.	**Rabih El Chammay**	M	**EMR**	Ministry of Health, Beirut, Lebanon	Public mental health, mental health policy, health equity
8.	**Suhaila Ghuloum**	F	**EMR**	Weill Cornell Medicine, Qatar Hamad Medical Corporation, Qatar	Mental health service planning, schizophrenia, psychiatric epidemiology
9.	**Oye Gureje**	M	**AFR**	Department of Psychiatry, University College Hospital, Ibadan, Nigeria	Global mental health; epidemiology; aging; health system strengthening; classification of mental disorders
10.	**Yueqin Huang**	F	**WPR**	National Clinical Research Center for Mental Disorders, Peking University Sixth Hospital, Peking University Institute of Mental Health, China	Psychiatry, child behavioural and developmental disorders, self-harm, suicide, depression
11.	**Asma Humayun**	F	**EMR**	Meditrina Health Care, Pakistan	Depression, psychosocial support and interventions for mental disorders

	Name	Gender	WHO Region	Affiliation	Area of expertise
12.	**Thomas Munk Laursen**	M	**EUR**	National Centre for Register-Based Research, Aarhus University, School of Business and Social Sciences, Institute of Economics and Business, Aarhus, Denmark	Research in schizophrenia and bipolar disorder
13.	**Mario Maj**	M	**EUR**	Department of Psychiatry, University of Naples, Italy	Research in bipolar disorder, psychiatric comorbidity, classification of mental disorders
14.	**Soontareeporn Meepring**	F	**WPR**	Department of Nursing, Faculty of Nursing, Naresuan University, Phitsanulok, Thailand	Physical health in people with SMD, technology in mental health
15.	**Shanthi Mendis**	F	**SEAR**	Independent consultant in Global Health, Sri Lanka	Noncommunicable diseases and cardiology, health policy development, capacity strengthening, implementation research particularly in low- and middle-income countries.
16.	**Dorairaj Prabhakaran**	M	**SEAR**	Centre for Chronic Conditions and Injuries and Vice President, Public Health Foundation of India, Haryana, India	Cardiovascular disease prevention, epidemiology, developmental origin, and biomarkers of cardiovascular diseases and diabetes
17.	**Martin Prince**	M	**EUR**	King's College London, Institute of Psychiatry, Psychology & Neuroscience, London, UK	Dementia, global mental health, guidelines development, dementia in LMIC
18.	**Thara Rangaswamy**	F	**SEAR**	Schizophrenia Research Foundation, Chennai, India	Mental health research, policy and advocacy
19.	**David Shiers**	M	**EUR**	Psychosis Research Unit, Greater Manchester Mental Health Trust, UK; Division of Psychology and Mental Health, University of Manchester, UK	Early intervention, physical health in people with SMD, health inequality
20.	**Ezra Susser**	M	**AMR**	Columbia University, 722 West 168th Street, New York, USA	Psychiatric epidemiology, research on course and outcome of schizophrenia, homelessness
21.	**Graham Thornicroft**	M	**EUR**	Health Service and Population Research Department, King's College London, Institute of Psychiatry, Psychology & Neuroscience, London, UK	Global mental health, guidelines development, mental health services research, mental health stigma, health equity.
22.	**Abe Fekadu Wassie**	M	**AFR**	Department of Psychiatry, College of Health Sciences, Addis Ababa University, Ethiopia	Psychopharmacological studies, service development, cultural aspects of depression, programme management

Annex 2. Assessment of conflict of interest

INDIVIDUALS INVOLVED IN ASSESSMENT OF CONFLICT OF INTEREST:

Shekhar Saxena, Director
Department of mental health and substance abuse
WHO headquarters

Tarun Dua, Programme manager
Department of mental health and substance abuse
WHO headquarters

Neerja Chowdhary, Technical officer
Department of mental health and substance abuse
WHO headquarters

To comply with WHO's Conflict of Interest Policy, the Secretariat followed the revised Guidelines for Declaration of Interests (WHO Experts)[1]. Declarations of interest (DoI) were requested from a) all GDG members b) all external partners involved in the evidence review process; c) all experts invited to review the evidence profiles.

A letter requesting completion of a DoI form and submission of a curriculum vitae was sent to all GDG members, the external review group and external partners. They were asked to agree to the publication of a summary of declarations in the guideline. The GDG members were also required to complete a confidentiality undertaking. Once received, the WHO Secretariat reviewed the DoIs as well as additional information (internet and bibliographic database search) and evaluated if there are any conflicts of interest and if so, whether these require a management plan.

In order to enhance its management of conflicts of interest as well as strengthen public trust and transparency in connection with WHO meetings and activities involving the provision of technical/normative advice, the names and brief biographies of members being considered for participation in the GDG were disclosed for public notice and comment prior to the meeting.

At the beginning of the GDG meeting, the DoI of each GDG member were presented and GDG members and external partners were asked to update their DoI with relevant changes by notifying the responsible technical officer.

[1] WHO Office of Compliance, Risk Management and Ethics (CRE) http://intranet.who.int/homes/cre/ethics/doiexperts/

The follow up and suggested actions agreed upon to manage the conflicts of interest declared are summarized below:

- If members declare interests that are relevant to the meeting, the WHO Secretariat will note any potential conflict of interest and summarize these and then decide whether and to what extent they can participate in the guideline development.
- If the conflict is deemed to be significant, the WHO Secretariat will decide if the conflict necessitates exclusion of that person from participating in the guideline process or if their participation should be limited.
- These decisions are made on a case-by-case basis.

Below is a summary of the declared conflicts of interest and how these were managed.

A. GDG MEMBERS

GDG Members with no relevant interests declared on the DOI form and no relevant interests found in the CV

1. **Abdullah Al-Khathami**
   Ministry of Health, Riyadh, Saudia Arabia.
2. **Corrado Barbui**
   University of Verona, Verona, Italy.
3. **Christopher Dowrick**
   University of Liverpool, Liverpool, United Kingdom.
4. **Benjamin Druss**
   Emory University, Atlanta, USA.
5. **Rahib El Chammay**
   National Mental Health Programme, Beirut, Lebanon.
6. **Suhaila Ghuloum**
   Weill Cornell Medicine, Doha, Qatar.
7. **Yueqin Huang**
   Peking University Institute of Mental Health, Beijing, China.
8. **Asma Humayun**
   Meditrina Healthcare, Islamabad, Pakistan.
9. **Mario Maj**
   University of Naples, Italy
10. **Soontareeporn Meepring**
    Naresuan University, Bangkok, Thailand.
11. **Shanthi Mendis**
    Colombo, Sri Lanka.
12. **Thomas Munk Laursen**
    Aarhus University, Aarhus, Denmark.
13. **Dorairaj Prabhakaran**
    Public Health Foundation of India, New Delhi, India.
14. **Thara Rangaswamy**
    Schizophrenia Research Foundation, Chennai, India
15. **Ezra Susser**
    Columbia University, New York, USA.

16. **Graham Thornicroft**
    King's College London, London, United Kingdom.
17. **Abe Fekadu Wassie**
    College of Health Sciences, Addis Ababa University, Ethiopia

GDG members who have declared an interest on the DOI form or where a potentially relevant interest has been noted from the CV

Jacqueline Curtis
University of New South Wales (UNSW), Sydney, Australia.

Dr Curtis received grants for research activities (three current grants amounting to a total of USD310,400 and three previous grants amounting to a total of USD16,600) from UNSW, New South Wales (NSW) government, commonwealth Bank of Australia and Prince of Wales Hospital, Sydney Foundation Patient Care Grant. She has been an expert advisor to the Orygen Youth Health (OYH) Research Centre, Melbourne for which she received USD440 remuneration in 2014. The OYH is part of the public mental health system in Melbourne, Australia, and sees young people aged 15 to 24, with a focus on early intervention and youth specific approaches. She also received honoraria for speaking at various scientific fora amounting to a total of USD5900 between 2014 and 2016 from the Adelaide Clinic, Tokyo Metropolitan Institute if Medical Science, Lundbeck, Townsville and Cairns Mental Health Services and OYH.

Action: *It was felt that this interest is insignificant or minimal and unlikely to affect, or be reasonably perceived to affect Dr Curtis's judgement in the development of the present guidelines. No further action was necessary.*

Gail L. Daumit
Johns Hopkins University School of Medicine, Baltimore, USA.

Dr Gail Lois Daumit is a Professor at Johns Hopkins Medical Institutions, Maryland, USA. In her DOI, she noted that the Johns Hopkins University School of Medicine received four Federal grants for research projects in which she is the principal investigator, with total annual direct costs of USD 1.7 million.

Action: *It was felt that this interest is insignificant or minimal and unlikely to affect, or be reasonably perceived to affect, Dr Daumit's judgement in the development of the present guidelines. No further action was necessary.*

Christopher Dowrick
University of Liverpool, Institute of Psychology, Health and Society

Dr Dowrick declared in his DOI form that as Chair of the Working Party for Mental Health of the World Organization of Family Doctors (WONCA) he has overseen the production and publication of a set of guidance documents and training materials for family doctors on the topic related to these guidelines.

Action: *It was felt that this interest is insignificant or minimal and unlikely to affect, or be reasonably perceived to affect, Dr Dowrick's judgement in the development of the present guidelines. He is deemed to be participating in the guideline development process in an individual capacity and not representing any organization. No further action was necessary.*

Oye Gureje
Department of Psychiatry University College Hospital, Ibadan, Nigeria.

Professor Oye Gureje is Professor of Psychiatry and Director, WHO Collaborating Centre for Research and Training in Mental Health, Neuroscience, Drug and Alcohol Abuse, University of Ibadan, Nigeria. In his DOI, he noted that he received research support amounting to $2.5million from the National Institute of Mental Health for a current project to study collaborative shared care for people with SMD.

Action: *It was felt that this interest is insignificant or minimal and unlikely to affect, or be reasonably perceived to affect, Professor Gureje's judgement in the development of the present guidelines. No further action was necessary.*

Martin Prince
King's College London, London, United Kingdom.

Professor Prince declared in his DOI form that he currently receives research support through a grant from the National Institute of Health Research (NIHR, UK) amounting to GBP 7 million over four years. Prof Prince is the PI and 20% of his salary costs are charged to the grant. The work focuses on health systems strengthening in sub Saharan Africa and one theme relates to the topic of these guidelines i.e. integrated primary healthcare for multimorbid conditions.

Action: *It was felt that this interest is insignificant or minimal and unlikely to affect, or be reasonably perceived to affect, Professor Prince's judgement in the development of the present guidelines. No further action was necessary.*

David Shiers
Healthy Active Lives (HeAL), Manchester, United Kingdom.

Dr David Shiers has honorary appointment with the Greater Manchester Mental Health NHS Foundation Trust and University of Manchester. In his DOI, he noted that he received remuneration as consultant the National Health Service, Royal College of Psychiatrists, NICE and Health Services Executive, Ireland for activities related to the subject of the meeting or the work. He also noted that he has received, along with other partners, a total of GBP 3.2 million funding for 6 research projects from the National Institute of Health Research, UK.

Action: *It was felt that this interest is insignificant or minimal and unlikely to affect, or be reasonably perceived to affect, Dr Shiers's judgement in the development of the present guidelines. No further action was necessary.*

B. EXTERNAL REVIEW GROUP

Members of the external review group with no relevant interests declared on the DOI form and no relevant interests found in the CV

1. **Atalay Alem**
   Department of Psychiatry, Faculty of Medicine, Addis Ababa University, Ethiopia
2. **Zipporah Ali**
   Kenya Hospices and Palliative Care Association, Kenya
3. **Lydia Chwastiak**
   University of Washington Medical Centre, USA
4. **Pim Cuijers**
   Vrije Universiteit Amsterdam, The Netherlands
5. **Alan Cohen**
   West London Mental Health Trust, UK
6. **Julian Eaton**
   CBM and the London School of Hygiene and Tropical Medicine, UK
7. **Alberto Minoletti**
   School of Public Health, Faculty of Medicine, University of Chile, Chile
8. **Rajat Ray**
   National Drug Dependence Treatment Centre, All India Institute of Medical Sciences, New Delhi, India
9. **Sarrafzadegan Nizal**
   Isfahan University of Medical Sciences in Iran and School of Population and Public Health in the University of British Columbia in Canada
10. **John Saunders**
    The University of Sydney, Australia;
11. **Najma Siddiqi**
    University of York, UK
12. **Isolde Sommers**
    Danube University Krems, Austria
13. **Héðinn Unnsteinsson**
    Prime Minister's Office, Iceland
14. **Pieter Ventevogel**
    UNHCR, Switzerland
15. **Lakshmi Vijaykumar**
    Voluntary Health Services, Chennai, India.

Members of the external review group who have declared an interest on the DOI form or where a potentially relevant interest has been noted from the CV

Ayesha Motala
University of KwaZulu-Natal, South Africa

Dr Motala declared that as a public servant working in a government institute, she seeks sponsorships to meetings from various organizations, especially when her scientific abstracts are accepted for presentations. The sponsorships are merely for attending the meetings, with no obligation to the sponsoring companies.

Details of such sponsorship for which she received a total amount of $26,000:

4-8 December 2017: International Diabetes Federation(IDF) Congress, Abu Dhabi: Sanofi Aventis sponsorship for travel and Accommodation; 11-15 September 2017: European Association for the Study of Diabetes(EASD) Congress, Lisbon: Pfizer sponsorship for Travel and accommodation; 8-13 June 2018: American Diabetes Association (ADA), San Diego: Boehringer Ingelheim sponsorship for Travel and accommodation: a member of her collaborating scientific team presented a paper.

Action: *It was felt that this interest is insignificant or minimal and unlikely to affect, or be reasonably perceived to affect, Dr Motala's contribution as an external reviewer for these guidelines. No further action was necessary.*

Charlene Sunkel
Central Gauteng Mental Health Society, South Africa

Ms Sunkel is a service user group representative and declared that she has published in the World Psychiatry journal on premature mortality of people with SMD titled: "A service users perspective" https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5269497/

Action: *It was felt that this interest is insignificant or minimal and unlikely to affect, or be reasonably perceived to affect, Ms Sunkel's contribution as an external reviewer for these guidelines. No further action was necessary.*

Inka Weissbecker
International Medical Corps, Washington DC, USA.

Dr Weissbecker works for International Medical Corps (IMC) which is a humanitarian non-profit organization and has an interest in the subject of mental health and distress related to humanitarian crises (as IMC has various global projects integrating mental health and psychosocial support). She has also worked as a consultant in the field of mental health in the past (more than 10 years ago) including for WHO.

Action: *It was felt that this interest is insignificant or minimal and unlikely to affect, or be reasonably perceived to affect, Dr Weissbecker's contribution as an external reviewer for these guidelines. No further action was necessary.*

C. EXTERNAL PARTNERS

External partners with no relevant interests declared on the DOI form and no relevant interests found in the CV

Maya Semrau
King's College London, London and Global Health and Infection Department, Brighton and Sussex Medical School, Brighton, United Kingdom.

External partners who have declared an interest on the DOI form or where a potentially relevant interest has been noted from the CV

Kavitha Kolappa
Harvard Medical School, Boston, USA

Dr Kolappa is part of the systematic review team for the development of these guidelines. Dr Kolappa declared that she received research support amounting to approximately USD 56,000 (USD 51,000 as stipend and USD 5000 for travel costs and purchase of computer) from the National Institutes of Health, USA. The period of this grant was for one year and ended in October 2017. Her area of study was the proposed relationship between social relationships, metabolic disease, and post-traumatic stress disorder.

Action: *It was felt that this interest is insignificant or minimal and unlikely to affect, or be reasonably perceived to affect, Dr Kolappa's contribution to the evidence review and synthesis process for the development of the present guidelines. As a member of the systematic review group she will be a technical resource and, therefore, will not participate in any of the closed sessions (voting or drafting final recommendations). No further action was necessary.*

Jayati Das-Munshi
King's College London, London, United Kingdom

Dr Das-Munshi is part of the systematic review team. In her DOI she noted that she is funded (amount GBP578198) by a Clinical Scientist Fellowship by a UK health charity, Health Foundation, in partnership with the Academy of Medical Sciences. She stated that the funder does not have any business or commercial interest in the work related to these guidelines and her research is independent of the funder's views.

Action: *It was felt that this interest is insignificant or minimal and unlikely to affect, or be reasonably perceived to affect, Dr Das-Munshi's contribution to the evidence review and synthesis process for the development of the present guidelines. As a member of the systematic review group she will be a technical resource and, therefore, will not participate in any of the closed sessions (voting or drafting final recommendations). No further action was necessary.*

Annex 3. Scoping questions

BACKGROUND QUESTIONS

1. Association of physical health conditions with SMD

What is the comorbidity between physical health conditions (NCDs and infectious diseases) and SMD?

What is the impact of physical health conditions on the morbidity and mortality of people with SMD?

PICO (POPULATION, INTERVENTION, COMPARISON, OUTCOME) QUESTIONS

2. Tobacco cessation

For people with SMD who use tobacco, are pharmacological (including nicotine replacement therapy, bupropion, varenicline) and/or non-pharmacological interventions effective to support tobacco cessation?

P: people with SMD who use tobacco

I: pharmacological interventions and/or non-pharmacological interventions:

- pharmacological interventions: including nicotine replacement therapy, bupropion, varenicline
- non-pharmacological interventions

C: care as usual and/or placebo

O:

- Critical
  - Tobacco cessation/abstinence rates
  - Tobacco consumption rates
  - Respiratory disease outcomes (COPD, asthma)
- Important
  - Frequency of adverse events/side-effects (including drug interactions)

3. Weight management

3.1 For people with SMD who are overweight or obese, are non-pharmacological and/or pharmacological interventions and/or pharmacological management strategies effective to support weight reduction?

P: people with SMD who are overweight or obese

I: non-pharmacological and/or pharmacological interventions and/or pharmacological management strategies:

- Non-pharmacological interventions: e.g. cognitive-behavioural intervention strategies, lifestyle interventions (e.g. diet, exercise, physical activity / decreased sedentary behaviour, health education), family involvement in interventions
- Pharmacological interventions: weight-loss medication (e.g. orlistat)
- Pharmacological management strategies: e.g. switching antipsychotic medication

C: care as usual and/or placebo

O:

- Critical
  - Change in weight
  - Mean BMI (kg/m2) or change in BMI
- Important
  - Reduced sedentary behaviour
  - Maintenance of weight change/ Attenuation/prevention of weight gain
  - Frequency of adverse events/side-effects

3.2 For people with SMD who are at risk of becoming overweight or obese, are non-pharmacological interventions effective to support prevention of weight gain?

P: people with SMD who are at risk of becoming overweight or obese, e.g. people who have just started anti-psychotic medication

I: non-pharmacological interventions, e.g. cognitive-behavioural intervention strategies, lifestyle interventions (e.g. diet, exercise, physical activity / decreased sedentary behaviour, health education), family involvement in interventions

C: care as usual

O:

- Critical
  - Change in weight
  - Mean BMI (kg/m2) or change in BMI
  - Maintenance of weight change
  - Attenuation/prevention of weight gain
- Important
  - Reduced sedentary behaviour
  - Frequency of adverse events/side-effects

4. Substance use disorders; drugs and/or alcohol

For people with SMD and substance (drug and/or alcohol) use disorder, are pharmacological and/or non-pharmacological interventions for substance use disorder effective to support reduction in substance use-related outcomes?

P: people with SMD and substance (drug and/or alcohol) use disorder

I: pharmacological and/or non-pharmacological interventions for substance use disorders:

- Pharmacological interventions
- Non-pharmacological interventions: e.g. motivational interviewing and/or CBT, psychoeducation, brief assessment interview, dual-focus interventions

C: care as usual / placebo or one treatment vs another

O:

- Critical
  - Level of consumption
  - Frequency of use
  - Abstinence
  - Relapse rates
- Important
  - Frequency of adverse events / side-effects

5. Cardiovascular disease / risk factors

5.1 For people with SMD and pre-existing cardiovascular disease, what pharmacological and/or non-pharmacological interventions are effective to support reduction of cardiovascular disease outcomes

P: people with SMD and pre-existing cardiovascular disease: e.g. coronary heart disease, prior heart failure or stroke, cardiomyopathy, congenital heart disease, peripheral vascular disease

I: pharmacological and/or non-pharmacological interventions:

- pharmacological interventions
- non-pharmacological interventions

C: one treatment versus another or care as usual/placebo

O:

- Critical
  - Major adverse cardiovascular event (MACE) - includes cardiovascular death, myocardial infarction, stroke, heart failure, hospitalization, amputation
- Important
  - Frequency of adverse events/side-effects

5.2 For people with SMD and cardiovascular risk factors (a. high blood pressure; b. high lipid levels), what pharmacological and/or non-pharmacological interventions are effective to support reduction of cardiovascular risk factors?

P: people with SMD and cardiovascular risk factors: a) high blood pressure (BP>140/90 mmHg; b) high lipid levels (e.g. cholesterol>200mg/dl or 5.2 mmol/l)

I: pharmacological and/or non-pharmacological interventions:

- pharmacological interventions: a) medication to control high blood pressure; b) medications for high lipid levels
- non-pharmacological interventions

C: one treatment versus another or care as usual/placebo

O:

- Critical
  - Adequacy of control of CVD risk factors (a. blood pressure <130/80mmHg; b. cholesterol <200mg/dl)
  - Cardiovascular disease incidence - MI, stroke, chronic cardiovascular disease
- Important
  - Frequency of adverse events/side-effects

6. Diabetes mellitus

For people with SMD and diabetes mellitus, what pharmacological and/or non-pharmacological interventions are effective to improve glycaemic control?

P: people with SMD and diabetes mellitus

I: pharmacological interventions and/or non-pharmacological interventions:

- pharmacological interventions: e.g. medication to treat diabetes
- non-pharmacological interventions: e.g. e.g. behavioural lifestyle interventions, cognitive behaviour therapy

C: one treatment versus another or care as usual

O:

- Critical
  - Fasting blood glucose <120mg/dl; post-prandial blood glucose<160mg/dl,
  - Glycosylated haemoglobin A1c (HbA1c<7 for people below 60 years and 7-8 for people above 60 years with other risk factors)
  - Diabetes complications – MACE, chronic kidney disease, diabetic retinopathy, diabetic neuropathy, hospitalization for infection
- Important
  - Frequency of adverse events / side-effects

7. HIV/AIDS

For people with SMD and HIV/AIDS, what pharmacological (i.e. ARV drugs, psychopharmacology) and nonpharmacological interventions are effective to support reduction in HIV-related outcomes?

P: people with SMD and HIV/AIDS

I:

- pharmacological interventions (ARV drugs, psychopharmacology)
- Nonpharmacological interventions

C: one treatment versus another or care as usual

O:

- Critical
  - HIV-related outcomes
- Important
  - Frequency of adverse events / side-effects

8. Other infectious diseases (Tuberculosis, Hepatitis B/C)

For people with SMD and infectious diseases (Tuberculosis, Hepatitis B/C), what pharmacological and nonpharmacological (social, psychological) interventions are effective for treatment of infectious diseases (i.e. tuberculosis, hepatitis B, hepatitis C)?

P: people with SMD and infectious diseases (Tuberculosis, Hepatitis B/C)

I:

- pharmacological interventions for infectious diseases
- Nonpharmacological (social, psychological) interventions for infectious diseases

C: one treatment versus another or care as usual

O:

- Critical
  - Infectious disease-related outcomes
- Important
  - Frequency of adverse events / side-effects

Annex 4. Background question: Association of physical health conditions with severe mental disorders

A. WHAT IS THE COMORBIDITY BETWEEN PHYSICAL HEALTH CONDITIONS (NCDS AND INFECTIOUS DISEASES) AND SMD?

A growing body of evidence has demonstrated the bi-directional relationships between SMD, including moderate to severe depression, bipolar disorder, as well as schizophrenia and other psychotic disorders, and physical health conditions including both non-communicable and infectious diseases.

SMD and non-communicable diseases (NCDs):

SMD and the major NCDs, including cardiovascular diseases, diabetes, respiratory illnesses, and cancers, are related in complex ways. From an epidemiological standpoint, mental disorder itself is a well-known risk factor for NCDs; its presence increases the chance that an individual will also suffer from one or more chronic illnesses. Overall, people with SMD have 1.53 times greater risk of cardiovascular disease and 1.85 times greater risk of death due to cardiovascular disease (Correll *et al.*, 2017). People with SMD, particularly those who have had multiple episodes of illness, also have higher rates of diabetes mellitus, with 1.85 times greater risk than the general population (Vancampfort *et al.*, 2016).

The reasons for the high co-morbidity between SMDs and NCDs have been extensively studied. People with SMD are more likely to engage in lifestyle behaviours that contribute to or exacerbate NCDs; that is, poor mental health is associated with the major modifiable risk factors for NCDs including tobacco use, harmful use of alcohol, unhealthy diets, and physical inactivity, which is elaborated further below. Additionally, pathophysiologically, persistent and SMD can affect and in turn, can be affected by stress-related NCDs (Watson *et al.*, 2017),(Kapczinski *et al.*, 2008; Nugent *et al.*, 2015). Furthermore, the iatrogenic effects of medicines used to treat SMDs are linked with increased risk of cardiometabolic diseases. Lastly, individuals with mental disorders are less likely to seek and receive screening and adequate treatment for NCDs, and symptoms may affect adherence to treatment as well as prognosis.

Tobacco consumption (Lasser *et al.*, 2000) is common amongst people with SMD and has been identified as a leading preventable cause of premature mortality in this population. Persons with schizophrenia and bipolar disorder are 5 times and 3 ½ times more likely to smoke currently than the general population, respectively (de Leon and Diaz, 2005),(Jackson *et al.*, 2015). ***Alcohol use disorders*** are also common amongst people with SMD, with one study using the national Danish registry finding the comorbidity of alcohol use disorder with schizo-phrenia, bipolar disorder, and depression to be approxi-mately 35%, 33%, and 23%, respectively. The comorbidity rates of ***all substance use disorders*** combined were even higher, with 48%, 40%, and 29% for schizophrenia, bipolar disorder, and de-pression, respectively (Jørgensen, Nordentoft and Hjorthøj, 2018).

Additionally, people with SMD are more likely to consume ***unhealthy diets*** and be ***physically inactive*** (Dipasquale *et al.*, 2013) (Jakobsen *et al.*, 2018) (Vancampfort *et al.*, 2017), which can lead to overweight, obesity, diabetes, and cardiovascular diseases. Overall, the risk of being ***overweight or obese*** as defined by a body mass index (BMI) of 25 or greater has been shown to be increased 3.4 fold for people with schizophrenia and 3.9 fold for people with bipolar disorder when compared with people without diagnoses of SMD (Gurpegui *et al.*, 2012). When considering obesity alone, as defined by a BMI of 30 or greater, the risk associated with schizophrenia and bipolar disorder jumps to 4.3 fold 4.6 fold, respectively (Gurpegui *et al.*, 2012).

Compounding the risks outlined above, the iatrogenic effects of psychotropic medications frequently used to treat the symptoms of SMD including antipsychotic medication (and to some extent, antidepressants and mood stabilizers) are linked with an increased risk of developing physical health conditions and associated complications (Correll *et al.*, 2015) (De Hert *et al.*, 2011) (Correll *et al.*, 2017). The use of antipsychotic medications has been associated with obesity, insulin resistance, diabetes, myocardial infarctions, atrial fibrillation, stroke, and death (Lieberman *et al.*, 2005) (Henderson *et al.*, 2005) (Chou *et al.*, 2017) (Sacchetti, Turrina and Valsecchi, 2010) (Yang *et al.*, 2018).

SMD and infectious diseases:

People with SMD are at greater risk than the general population for exposure to infectious diseases, including HIV, tuberculosis (TB) and chronic hepatitis. In the US, for example, persons with SMD were found to have a 10-fold higher prevalence of HIV (Hughes *et al.*, 2016). In a population-wide study in Sweden, persons with SMD when compared with the general population were found to have approximately 2.6 times greater risk of HIV infection, as well as 2.3 and 6.1 times greater risk of hepatitis B and C infections, respectively (Bauer-Staeb *et al.*, 2017). Further, one country-wide study in Taiwan revealed that persons with schizophrenia have a 1.5 times greater risk for tuberculosis infections than that of the rest of the population (Kuo *et al.*, 2013).

As is seen with NCDs, there is a bi-directionality of the association between SMD and infectious diseases. HIV virus and opportunistic infections associated with AIDS can cause neurological damage, while mental disorders can also arise as a side effect of antiretroviral treatment or from the stigma, stress and socio-economic predicaments associated with the infection and treatment process. There are widespread discriminatory attitudes and behaviours towards people with HIV, TB and Hepatitis B/C in the community where they reside, particularly in developing countries. The psychological distress associated with stigma and discrimination may also trigger or aggravate the symptoms of SMD in affected individuals.

B. WHAT IS THE IMPACT OF PHYSICAL HEALTH CONDITIONS ON THE MORBIDITY AND MORTALITY OF PEOPLE WITH SMD?

The mortality gap for people with SMD:

People with SMD, including moderate to severe depression, bipolar disorder, as well as schizophrenia and other psychotic disorders, have a 2-3 times higher average mortality compared to the general population, which translates to a 10-20 year reduction in life expectancy (Liu *et al.*, 2017). Patients with bipolar disorder and schizophrenia have been shown to have higher rates of mortality in both high and low-income settings (Tsuang, Woolson and Fleming, 1980) (Capasso *et al.*, 2008) (Laursen, 2011) (Nielsen *et al.*, 2013) (Fekadu *et al.*, 2015) (Krupchanka *et al.*, 2018). One prospective cohort-study in Ethiopia, for example, found the overall standardized mortality ratio (SMR) of patients with SMD (schizophrenia, bipolar disorder, or severe depression) to be twice that of the general population, with schizophrenia associated with the highest risk (SMR three times that of the general population) (Fekadu *et al.*, 2015). Moreover, for schizophrenia in particular, the mortality gap appears to be widening over time (Saha, Chant and McGrath, 2007). While people with SMD do have higher rates of death due to unnatural causes (accidents, homicide, or suicide) than the general population, the majority of deaths amongst people with SMD are attributable to comorbid physical health conditions, both non-communicable and communicable (Liu *et al.*, 2017). Mortality in people with SMD is far higher in individuals with substance use disorders than in those without. It has been shown that alcohol use disorders as a comorbid condition to SMD doubled risk of all-cause mortality (Hjorthøj *et al.*, 2015).

The reasons for the mortality gap in people with SMD:

Numerous potential causes have been proposed for the increased mortality of patients with SMD including the well-known bidirectional relationship between mental disorders and other NCDs as elaborated above; differential exposure to risk factors driving the development of NCDs; iatrogenic effects of medications for SMD; increased risk for infectious diseases; comorbid substance use disorders; and inequitable access to health care services.

Equitable access to comprehensive health services remains out of reach for the majority of people with SMD. Unfortunately, people with SMD often lack access to health services or receive poor quality care, spanning from promotion and prevention, screening, and treatment (De Hert *et al.*, 2011). Despite the elevated risks facing persons with SMD, screening for infectious illnesses such as HIV is poor (Mangurian *et al.*, 2017) (Senn and Carey, 2009). Screening for metabolic risk factors for persons with SMD, as well as those receiving antipsychotic medications also remains abysmal in low and high-income settings (Saloojee, Burns and Motala, 2014) (Morrato *et al.*, 2009) (Barnes *et al.*, 2007). Further, persons with SMD may not receive the life-saving care that they need. A large retrospective cohort analysis in the US found that when compared with people without mental disorder, people with schizophrenia were not even half as likely to receive cardiac catheterization after a heart attack (Druss *et al.*, 2000). It is crucial to address the disparities in health care access and provision for people with SMD. Recognizing the frequent comorbidity between mental and physical health conditions, specific recommendations addressing the physical conditions causing the increased morbidity and mortality of people with SMD are needed. In some instances, treatment recommendations for the general population may need to be adapted for people with SMD. Non-pharmacological interventions might warrant tailoring to account for cognitive, motivational, and social needs of people with SMD, and the benefits and risks of pharmacological interventions will need to be balanced against the potential side effects and drug-drug interactions between proposed interventions and psychotropic medications commonly used for SMD.

Annex 4. References

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Annex 5. Evidence review methodology

Comprehensive searches of major bibliographic databases were conducted in order to identify one or more systematic reviews that matched each of the outcomes for each of the PICO questions. The aim was to identify systematic reviews that were timely, of high quality and relevant to each of the PICO questions.

THE FOLLOWING PROCESS WAS EMPLOYED FOR THE SEARCHES:

1. Searched for systematic reviews (including meta-analyses) that were published in the last five years for each of the PICO questions. Guidelines from the last five years were also included, if these closely matched the population to whom the PICO question applies; any guidelines used needed to adhere to the WHO rules for guidelines. The searches were run in February 2018.

2. If no relevant high-quality systematic reviews were identified from the last five years for any of the PICO questions, the search was expanded to include systematic reviews from the last ten years for that PICO question. This was the case for the two PICO questions on HIV/AIDS and other infectious diseases; these searches were re-run in March 2018.

3. Where relevant, any guidelines that did not closely match the population to whom the PICO question applied (e.g. guidelines that apply to the general population) were used as indirect evidence.

4. For the PICO question on substance use disorder, based on the GDG's feedback during the GDG meeting in May 2018, the searches were expanded to include further search terms and were re-run in June 2018 (searching for systematic reviews from the last five years).

The following bibliographic databases were searched:

- Cochrane Library (including DARE) (title, abstract, keywords + mesh terms)
- PubMed/Medline (all fields)
- EMBASE (Ovid)
- PSYCINFO (anywhere)
- Epistemonikos (title/abstract)
- Global Health Library (title/abstract/subject)
- For those PICO questions where the search was expanded (see step 2 above), the National Guideline Clearing House was also searched.

After the searches were run using the search strategies listed on the pages below, titles and abstracts of all results were screened in Endnote; subsequently the full texts of those papers were reviewed that could not be excluded based on the title/abstract review.

GRADE EVIDENCE TABLES

All systematic reviews / meta-analyses that were identified as matching one of the PICO questions based on the search strategy described above were then assessed using the AMSTAR methodology[2], which evaluates the quality of systematic reviews using eleven criteria.

For each outcome of each PICOquestion, one or more systematic reviews were then selected to be used within the GRADE evidence tables for the PICO questions' evidence profiles. The following criteria were used when selecting which systematic review to use within the GRADE evidence tables:

- Published in the last five years, ideally three years (timeliness)
- High quality (i.e. at least six, but ideally more, of the eleven criteria of the AMSTAR scored positively)
- Closely relevant to the PICO
- Systematic reviews that dealt with SMD generally (rather than specific mental disorders) given preference
- Comprehensive systematic reviews given preference, where possible
- Cochrane reviews or other meta-analyses given preference, where possible/appropriate

The GRADE methodology involves rating the quality of the studies included in the systematic review according to study design, risk of bias, inconsistency, indirectness, imprecision, and publication bias. Together with the effect sizes of studies, an overall 'certainty of evidence' is provided of either very low, low, moderate or high.

GRADE evidence tables were completed using the GRADEpro online tool[3]; the same criteria were used as for the mhGAP Intervention Guide when completing the GRADE evidence tables in terms of the assessment of the quality of studies (for risk of bias, inconsistency, indirectness, imprecision, and publication bias)[4].

[2] Shea BJ, Grimshaw JM, Wells GA, Boers M, Andersson N, Hamel C et al. Development of AMSTAR: a measurement tool to assess the methodological quality of systematic reviews. *BMC Medical Research Methodology.* 2007; 7:10

[3] https://gradepro.org/

[4] See http://www.who.int/mental_health/mhgap/evidence/mhgap_guideline_process_2009.pdf

SEARCH STRATEGIES

Separate searches were performed for each of the seven PICO questions. Where PICO questions included both pharmacological and non-pharmacological interventions, searches were run separately for these.

The three search sets outlined below for each of the PICO questions were separated by an 'AND' when running the searches.

Filters were used in the bibliographic databases where possible to restrict the searches to systematic reviews and meta-analyses, as well as to humans. No further restrictions were employed, for example in terms of language (apart from the publication date, as mentioned above).

The 'Advanced Search' option was selected in bibliographic databases, where possible.

PICO QUESTION 2

For people with SMD who are use tobacco, are pharmacological (including nicotine replacement therapy, bupropion, varenicline) interventions effective to support tobacco cessation?

Search #1: SMD

(exp Mental Disorders/ OR exp Psychotic Disorders/ OR exp Bipolar and Related Disorders/ OR exp Depressive Disorder) OR

((Mental AND (disorder* OR disabilit* OR illness OR "health condition" OR "health problem" OR distress)) OR "psychological distress" OR "psychiatric disorder") OR

((schizophrenia OR schizophrenic) OR Schizotyp* OR ((Delusional OR paranoid) AND disorder*) OR hallucination* OR Psychotic OR Schizoaffective OR psychosis) OR

(((manic OR bipolar OR mood) AND disorder*) OR (depressive AND (disorder* OR episode*)) OR "depressive symptom*" OR hypomania OR mania* OR ((major OR psychotic OR disorder*) AND depression))

Search #2: smoking

(exp Smoking/ OR exp Smokers/ OR exp Tobacco Smoking/ OR exp Tobacco Use/ OR exp Tobacco/ OR exp Nicotine/) OR

(smok* OR tobacco OR nicotin* OR cigarette*)

Search #2: smoking

(exp Smoking/ OR exp Smokers/ OR exp Tobacco Smoking/ OR exp Tobacco Use/ OR exp Tobacco/ OR exp Nicotine/) OR

(smok* OR tobacco OR nicotin* OR cigarette*)

Search #3: pharmacological tobacco cessation interventions

(exp Smoking Cessation/ OR exp Smoking Reduction/ OR exp Tobacco Use Cessation/ OR exp Tobacco Use Cessation Products/ OR exp Bupropion/ OR exp Varenicline/ OR exp Nicotine Chewing Gum) OR

(exp Drug Therapy/ OR exp Pharmacology/ OR exp Psychopharmacology/ OR exp Metabolic Side Effects of Drugs and Substances/ OR exp Pharmacologic Actions/ OR exp Drug Effects/ OR exp Psychotropic Drugs/) OR

((drug* OR pharmac* OR medic* OR psychotrop*) AND (intervent* OR therap* OR treat* OR care OR servic*)) OR (drug* OR medic*) OR

((smok* OR tobacco OR nicotin* OR cigarette*) AND (cessation OR reduc* OR abst*)) OR

(bupropion OR varenicline OR "nicotine replacement therapy" OR "nicotine gum" OR "nicotine patch")

For people with SMD who are use tobacco, are non-pharmacological interventions effective to support tobacco cessation?

Search #1: SMD

(exp Mental Disorders/ OR exp Psychotic Disorders/ OR exp Bipolar and Related Disorders/ OR exp Depressive Disorder) OR

((Mental AND (disorder* OR disabilit* OR illness OR “health condition” OR “health problem” OR distress)) OR "psychological distress" OR "psychiatric disorder") OR

((schizophrenia OR schizophrenic) OR Schizotyp* OR ((Delusional OR paranoid) AND disorder*) OR hallucination* OR Psychotic OR Schizoaffective OR psychosis) OR

(((manic OR bipolar OR mood) AND disorder*) OR (depressive AND (disorder* OR episode*)) OR "depressive symptom*" OR hypomania OR mania* OR ((major OR psychotic OR disorder*) AND depression))

Search #2: smoking

(exp Smoking/ OR exp Smokers/ OR exp Tobacco Smoking/ OR exp Tobacco Use/ OR exp Tobacco/ OR exp Nicotine) OR

(smok* OR tobacco OR nicotin* OR cigarette*)

Search #3: non-pharmacological tobacco cessation interventions

(exp Smoking Cessation/ OR exp Smoking Reduction/ OR exp Tobacco Use Cessation/OR exp Tobacco Use Cessation Products/) OR

(exp Exercise Therapy/ OR exp Therapy/ OR exp Therapeutics/ OR exp Family Therapy/ OR exp Psychotherapy/ OR exp Cognitive Therapy/ OR exp Behaviour Therapy/ OR exp Counseling/ OR exp Mental Health Services/ OR exp Problem Based Learning/ OR exp Problem Solving/) OR

((psychosocial OR psycho* OR lifestyle* OR cognit* OR behaviour* OR behaviour* OR non-pharmac*) AND (intervent* OR therap* OR treat* OR care OR servic*)) OR

(“problem solving” OR psychoeducation OR couns*) OR

((smok* OR tobacco OR nicotin* OR cigarette*) AND (cessation OR reduc* OR abst*))

PICO QUESTIONS 3.1 & 3.2

For people with SMD who are overweight or obese, are pharmacological interventions effective to support weight reduction?

Search #1: SMD

(exp Mental Disorders/ OR exp Psychotic Disorders/ OR exp Bipolar and Related Disorders/ OR exp Depressive Disorder) OR

((Mental AND (disorder* OR disabilit* OR illness OR “health condition” OR “health problem” OR distress)) OR "psychological distress" OR "psychiatric disorder") OR

((schizophrenia OR schizophrenic) OR Schizotyp* OR ((Delusional OR paranoid) AND disorder*) OR hallucination* OR Psychotic OR Schizoaffective OR psychosis) OR

(((manic OR bipolar OR mood) AND disorder*) OR (depressive AND (disorder* OR episode*)) OR "depressive symptom*" OR hypomania OR mania* OR ((major OR psychotic OR disorder*) AND depression))

Search #2: overweight

(exp Overweight/ OR exp Obesity/) OR

(“overweight” OR obes* OR “weight-related side-effects” OR “weight gain”)

Search #3: pharmacological interventions for weight reduction

(exp Obesity Management/ OR exp Anti-Obesity Agents/ OR exp Body Weight Changes/ OR exp Body Weight Maintenance/ OR exp Weight Reduction Programs/) OR

(exp Drug Therapy/ OR exp Pharmacology/ OR exp Psychopharmacology/ OR exp Metabolic Side Effects of Drugs and Substances/ OR exp Pharmacologic Actions/ OR exp Drug Effects/ OR exp Psychotropic Drugs/) OR

((drug* OR pharmac* OR medic* OR psychotrop*) AND (intervent* OR therap* OR treat* OR care OR servic)) OR (drug* OR medic*) OR

((weight OR BMI OR “body mass*” OR fat* OR waist*) AND (loss OR reduc* OR maint*)) OR (“weight gain” AND (prevent* OR manag*)) OR

(orlistat OR “appetite suppressant*”)

For people with SMD who are overweight or obese, are pharmacological management strategies effective to support weight reduction?

Search #1: SMD

(exp Mental Disorders/ OR exp Psychotic Disorders/ OR exp Bipolar and Related Disorders/ OR exp Depressive Disorder) OR

((Mental AND (disorder* OR disabilit* OR illness OR "health condition" OR "health problem" OR distress)) OR "psychological distress" OR "psychiatric disorder") OR

((schizophrenia OR schizophrenic) OR Schizotyp* OR ((Delusional OR paranoid) AND disorder*) OR hallucination* OR Psychotic OR Schizoaffective OR psychosis) OR

(((manic OR bipolar OR mood) AND disorder*) OR (depressive AND (disorder* OR episode*)) OR "depressive symptom*" OR hypomania OR mania* OR ((major OR psychotic OR disorder*) AND depression))

Search #2: overweight

(exp Overweight/ OR exp Obesity/) OR

("overweight" OR obes* OR "weight-related side-effects" OR "weight gain")

Search #3: pharmacological interventions for weight reduction

(exp Obesity Management/ OR exp Anti-Obesity Agents/ OR exp Body Weight Changes/ OR exp Body Weight Maintenance/ OR exp Weight Reduction Programs/) OR

(exp Drug Therapy/ OR exp Pharmacology/ OR exp Psychopharmacology/ OR exp Metabolic Side Effects of Drugs and Substances/ OR exp Pharmacologic Actions/ OR exp Drug Effects/ OR exp Psychotropic Drugs/) OR

((drug* OR pharmac* OR medic* OR psychotrop*) AND (intervent* OR therap* OR treat* OR care OR servic)) OR (drug* OR medic*) OR

((weight OR BMI OR "body mass*" OR fat* OR waist*) AND (loss OR reduc* OR maint*)) OR ("weight gain" AND (prevent* OR manag*)) OR

(switch* AND (medic* OR drug*))

For people with SMD who are overweight or obese, are non-pharmacological interventions effective to support weight reduction?

For people with SMD who are at risk of becoming overweight or obese, are non-pharmacological interventions effective to support prevention of weight gain?

Search #1: SMD

(exp Mental Disorders/ OR exp Psychotic Disorders/ OR exp Bipolar and Related Disorders/ OR exp Depressive Disorder) OR

((Mental AND (disorder* OR disabilit* OR illness OR "health condition" OR "health problem" OR distress)) OR "psychological distress" OR "psychiatric disorder") OR

((schizophrenia OR schizophrenic) OR Schizotyp* OR ((Delusional OR paranoid) AND disorder*) OR hallucination* OR Psychotic OR Schizoaffective OR psychosis) OR

(((manic OR bipolar OR mood) AND disorder*) OR (depressive AND (disorder* OR episode*)) OR "depressive symptom*" OR hypomania OR mania* OR ((major OR psychotic OR disorder*) AND depression))

Search #2: overweight

(exp Overweight/ OR exp Obesity/) OR

("overweight" OR obes* OR "weight-related side-effects" OR "weight gain")

Search #3: non-pharmacological intervention for weight reduction and prevention

(exp Obesity Management/ OR exp Nutrition Therapy/ OR exp Body Weight Changes/ OR exp Body Weight Maintenance/ OR exp Weight Reduction Programs/ OR exp Health Promotion/ OR exp Diet/ OR exp Risk Reduction Behaviour/ OR Risk Management/ OR exp Health Risk Behaviours/ OR exp Risk Factors/ OR exp Risk-Taking/) OR

(exp Exercise Therapy/OR exp Therapy/ OR exp Therapeutics/ OR exp Family Therapy/ OR exp Psychotherapy/ OR exp Cognitive Therapy/ OR exp Behaviour Therapy/ OR exp Counseling/ OR exp Mental Health Services/ OR exp Problem Based Learning/ OR exp Problem Solving/) OR

(exp Preventive Health Services/) OR

((psychosocial OR psycho* OR lifestyle* OR cognit* OR behaviour* OR behaviour* OR non-pharmac*) AND (intervent* OR therap* OR treat* OR care OR servic*)) OR

(problem solving OR psychoeducation OR couns*) OR

((weight OR BMI OR body mass* OR fat* OR waist*) AND (loss OR reduc* OR maint*)) OR (weight gain AND (prevent* OR manag*)) OR

(diet* OR nutrition* OR exercis* OR sport* OR physical activit* OR health promot* OR self-monit* OR calor* OR healthy eating OR food intake)

PICO QUESTIONS 4

For people with SMD and substance (drug and/or alcohol) use disorder, are pharmacological interventions for substance use disorder effective to support reduction in substance use-related outcomes?

Search #1: SMD

(exp Mental Disorders/ OR exp Psychotic Disorders/ OR exp Bipolar and Related Disorders/ OR exp Depressive Disorder) OR

((Mental AND (disorder* OR disabilit* OR illness OR “health condition” OR “health problem” OR distress)) OR "psychological distress" OR "psychiatric disorder") OR

((schizophrenia OR schizophrenic) OR Schizotyp* OR ((Delusional OR paranoid) AND disorder*) OR hallucination* OR Psychotic OR Schizoaffective OR psychosis) OR

(((manic OR bipolar OR mood) AND disorder*) OR (depressive AND (disorder* OR episode*)) OR "depressive symptom*" OR hypomania OR mania* OR ((major OR psychotic OR disorder*) AND depression))

Search #2: Substance use disorder

(exp Narcotics/ OR exp Substance-Related Disorders/ OR exp Alcoholism/ OR exp Alcoholics/ OR exp Alcohol Related-Disorders/ OR exp Drug Users/ OR exp Drug Misuse/ OR exp Street Drugs/ OR exp Nonprescription Drugs/ OR exp Drug-Seeking Behaviour/ OR exp substance abuse, intravenous/) OR

("drug abuse" OR "drug addict*" OR "drug depend*” OR "drug withdrawal" OR "drug misuse") OR

("addictive disease*" OR "addictive disorder*" OR addiction OR addictive OR "substance abuse" OR “substance misuse” OR "withdrawal syndrome" OR psychoactive*) OR

("alcoholic patient*" OR "alcoholic subject*" OR alcoholism OR "alcohol depend*" OR "fetal alcohol*" OR "prenatal alcohol*" OR "chronic ethanol*" OR "chronic* alcohol*" OR "alcohol withdrawal" OR "ethanol withdrawal" OR “excessive alcohol consumption” OR “alcohol use disorder” OR “alcohol misuse” OR “alcohol abuse”) OR

((cocaine OR heroin OR cannabis OR marijuana OR mdma OR methylenedioxymethamphetamin* OR ecstasy OR morphine* OR amphetamin* OR methamphetamin* OR opioid* OR opiat* OR “prescription drug*” OR “illegal drug*” OR “illicit drug*" OR “street drug” OR benzodiazepin* OR tranquiliz* OR narcot* OR methadone OR fentanyl) AND (abuse OR misuse OR depend* OR addict* OR withdrawal OR overdose OR intoxication OR “harmful use”)) OR

(“injecting drug use” OR IDU$1 OR IVDU$1 OR PWID$1 OR “injecting drug” OR “intravenous drug” OR “injecting substance” OR “intravenous substance”)

Search #3: pharmacological interventions for substance use disorders

(exp Substance Abuse Treatment Centers/ OR exp Alcohol Abstinence/) OR

(exp Drug Therapy/ OR exp Pharmacology/ OR exp Psychopharmacology/ OR exp Metabolic Side Effects of Drugs and Substances/ OR exp Pharmacologic Actions/ OR exp Drug Effects/ OR exp Psychotropic Drugs/) OR

(exp buprenorphine/ OR exp methadone/ OR exp opiate substitution treatment/ OR exp buprenorphine, naloxone drug combination/) OR

((drug* OR pharmac* OR medic* OR psychotrop*) AND (intervent* OR therap* OR treat* OR care OR servic*)) OR (drug* OR medic*) OR

(methadone OR buprenorphine OR naloxone OR naltrexone OR disulfiram OR nalmefene OR thiamine OR clonidine OR lofexidine OR acamprosate OR baclofen) OR

("opioid agonist maintenance treatment" OR OST OR MMT OR BMT OR "opioid substitution treatment" OR "methadone" OR "methadone maintenance" OR "buprenorphine" OR "buprenorphine maintenance" OR "opioid replacement")

For people with SMD and substance (drug and/or alcohol) use disorder, are non-pharmacological interventions for substance use disorder effective to support reduction in substance use-related outcomes?

Search #1: SMD

(exp Mental Disorders/ OR exp Psychotic Disorders/ OR exp Bipolar and Related Disorders/ OR exp Depressive Disorder) OR

((Mental AND (disorder* OR disabilit* OR illness OR "health condition" OR "health problem" OR distress)) OR "psychological distress" OR "psychiatric disorder") OR

((schizophrenia OR schizophrenic) OR Schizotyp* OR ((Delusional OR paranoid) AND disorder*) OR hallucination* OR Psychotic OR Schizoaffective OR psychosis) OR

(((manic OR bipolar OR mood) AND disorder*) OR (depressive AND (disorder* OR episode*)) OR "depressive symptom*" OR hypomania OR mania* OR ((major OR psychotic OR disorder*) AND depression))

Search #2: Substance use disorder

(exp Narcotics/ OR exp Substance-Related Disorders/ OR exp Alcoholism/ OR exp Alcoholics/ OR exp Alcohol Related-Disorders/ OR exp Drug Users/ OR exp Drug Misuse/ OR exp Street Drugs/ OR exp Nonprescription Drugs/ OR exp Drug-Seeking Behaviour/ OR exp substance abuse, intravenous/) OR

("drug abuse" OR "drug addict*" OR "drug depend*" OR "drug withdrawal" OR "drug misuse") OR

("addictive disease*" OR "addictive disorder*" OR addiction OR addictive OR "substance abuse" OR "substance misuse" OR "withdrawal syndrome" OR psychoactive*) OR

("alcoholic patient*" OR "alcoholic subject*" OR alcoholism OR "alcohol depend*" OR "fetal alcohol*" OR "prenatal alcohol*" OR "chronic ethanol*" OR "chronic* alcohol*" OR "alcohol withdrawal" OR "ethanol withdrawal" OR "excessive alcohol consumption" OR "alcohol use disorder" OR "alcohol misuse" OR "alcohol abuse") OR

((cocaine OR heroin OR cannabis OR marijuana OR mdma OR methylenedioxymethamphetamin* OR ecstasy OR morphine* OR amphetamin* OR methamphetamin* OR opioid* OR opiat* OR "prescription drug*" OR "illegal drug*" OR "illicit drug*" OR "street drug" OR benzodiazepin* OR tranquiliz* OR narcot* OR methadone OR fentanyl) AND (abuse OR misuse OR depend* OR addict* OR withdrawal OR overdose OR intoxication OR "harmful use")) OR

("injecting drug use" OR IDU$1 OR IVDU$1 OR PWID$1 OR "injecting drug" OR "intravenous drug" OR "injecting substance" OR "intravenous substance")

Search #3: non-pharmacological interventions for substance use disorders

(exp Substance Abuse Treatment Centers/ OR exp Alcohol Abstinence/ OR exp Needle-Exchange Programs/) OR

(exp Exercise Therapy/ OR exp Occupational Therapy/ OR exp Therapy/ OR exp Therapeutics/ OR exp Family Therapy/ OR exp Psychotherapy/ OR exp Cognitive Therapy/ OR exp Behaviour Therapy/ OR exp Counseling/ OR exp Mental Health Services/ OR exp Problem Based Learning/ OR exp Problem Solving/ OR exp harm reduction/) OR

((psychosocial OR psycho* OR lifestyle* OR cognit* OR behaviour* OR behaviour* OR non-pharmac*) AND (intervent* OR therap* OR treat* OR care OR servic*)) OR

("problem solving" OR psychoeducation OR couns*) OR

("motivational interviewing" OR "motivational enhancement therapy" OR MET OR CBT OR "cognitive behavioural therapy" OR "cognitive behavioural therapy" OR "brief assessment interview" OR "contingency management" OR "social skills training" OR "relapse prevention" OR "case management" OR "assertive community treatment" OR "family interventions") OR

(SBIRT OR "screening and brief interventions" OR outreach OR "residential programmes" OR "recovery management" OR "mutual self-help group" OR "Alcoholic Anonymous" OR "Narcotic Anonymous") OR

("harm reduction" OR NSP$1 OR NSEP$1 OR "needle syringe program$" OR "needle syringe exchange program$" OR "needle exchange$1" OR "syringe exchange $1")

PICO QUESTIONS 5.1 AND 5.2

For people with SMD and pre-existing cardiovascular disease, what pharmacological interventions are effective to support reduction of cardiovascular disease outcomes?

For people with SMD and cardiovascular risk factors (a. high blood pressure; b. high lipid levels), what pharmacological interventions are effective to support reduction of cardiovascular risk factors?

Search #1: SMD

(exp Mental Disorders/ OR exp Psychotic Disorders/ OR exp Bipolar and Related Disorders/ OR exp Depressive Disorder) OR

((Mental AND (disorder* OR disabilit* OR illness OR "health condition" OR "health problem" OR distress)) OR "psychological distress" OR "psychiatric disorder") OR

((schizophrenia OR schizophrenic) OR Schizotyp* OR ((Delusional OR paranoid) AND disorder*) OR hallucination* OR Psychotic OR Schizoaffective OR psychosis) OR

(((manic OR bipolar OR mood) AND disorder*) OR (depressive AND (disorder* OR episode*)) OR "depressive symptom*" OR hypomania OR mania* OR ((major OR psychotic OR disorder*) AND depression))

Search #2: cardiovascular disease / risk factors

(exp Cardiovascular Diseases/) OR

("heart disease" OR "heart attack*" OR stroke* OR "myocardial infarction" OR "transient ischemic attack" OR "cerebrovascular disease" OR "congestive heart failure" OR "vascular disease") OR

("cardiovascular risk*" OR ((high OR abnormal OR elevat*) AND ("blood pressure" OR cholesterol OR "blood glucose")))

Search #3: pharmacological interventions for cardiovascular disease/risk

(exp Cardiac Rehabilitation/ OR exp Risk Reduction Behaviour/ OR exp Risk Management/ OR exp Health Risk Behaviours/ OR exp Risk Factors/ OR exp Risk-Taking/) OR

(exp Drug Therapy/ OR exp Pharmacology/ OR exp Psychopharmacology/ OR exp Metabolic Side Effects of Drugs and Substances/ OR exp Pharmacologic Actions/ OR exp Drug Effects/ OR exp Psychotropic Drugs/) OR

((drug* OR pharmac* OR medic* OR psychotrop*) AND (intervent* OR therap* OR treat* OR care OR servic)) OR (drug* OR medic*) OR

(exp Preventive Health Services/) OR

(switch* AND (medic* OR drug*))

For people with SMD and pre-existing cardiovascular disease, what non-pharmacological interventions are effective to support reduction of cardiovascular disease outcomes?

For people with SMD and cardiovascular risk factors (a. high blood pressure; b. high lipid levels), what non-pharmacological interventions are effective to support reduction of cardiovascular risk factors?

Search #1: SMD

(exp Mental Disorders/ OR exp Psychotic Disorders/ OR exp Bipolar and Related Disorders/ OR exp Depressive Disorder) OR

((Mental AND (disorder* OR disabilit* OR illness OR "health condition" OR "health problem" OR distress)) OR "psychological distress" OR "psychiatric disorder") OR

((schizophrenia OR schizophrenic) OR Schizotyp* OR ((Delusional OR paranoid) AND disorder*) OR hallucination* OR Psychotic OR Schizoaffective OR psychosis) OR

(((manic OR bipolar OR mood) AND disorder*) OR (depressive AND (disorder* OR episode*)) OR "depressive symptom*" OR hypomania OR mania* OR ((major OR psychotic OR disorder*) AND depression))

Search #2: cardiovascular disease / risk factors

(exp Cardiovascular Diseases/) OR

("heart disease" OR "heart attack* OR stroke* OR "myocardial infarction" OR "transient ischemic attack" OR "cerebrovascular disease" OR "congestive heart failure" OR "vascular disease") OR

("cardiovascular risk*" OR (("high OR abnormal OR elevat*) AND ("blood pressure" OR cholesterol OR "blood glucose")))

Search #3: non-pharmacological interventions for cardiovascular disease/risk

(exp Cardiac Rehabilitation/ OR exp Risk Reduction Behaviour/ OR exp Risk Management/ OR exp Health Risk Behaviours/ OR exp Risk Factors/ OR exp Risk-Taking/OR exp Health Promotion/) OR

(exp Exercise Therapy/OR exp Therapy/ OR exp Therapeutics/ OR exp Family Therapy/ OR exp Psychotherapy/ OR exp Cognitive Therapy/ OR exp Behaviour Therapy/ OR exp Counseling/ OR exp Mental Health Services/ OR exp Problem Based Learning/ OR exp Problem Solving/) OR

((psychosocial OR psycho* OR lifestyle* OR cognit* OR behaviour* OR behaviour* OR non-pharmac*) AND (intervent* OR therap* OR treat* OR care OR servic*)) OR

("problem solving" OR psychoeducation OR couns*) OR

(exp Preventive Health Services/)

PICO QUESTION 6

For people with SMD and diabetes mellitus, what pharmacological interventions are effective to improve glycaemic control?

Search #1: SMD

(exp Mental Disorders/ OR exp Psychotic Disorders/ OR exp Bipolar and Related Disorders/ OR exp Depressive Disorder) OR

((Mental AND (disorder* OR disabilit* OR illness OR "health condition" OR "health problem" OR distress)) OR "psychological distress" OR "psychiatric disorder") OR

((schizophrenia OR schizophrenic) OR Schizotyp* OR ((Delusional OR paranoid) AND disorder*) OR hallucination* OR Psychotic OR Schizoaffective OR psychosis) OR

(((manic OR bipolar OR mood) AND disorder*) OR (depressive AND (disorder* OR episode*)) OR "depressive symptom*" OR hypomania OR mania* OR ((major OR psychotic OR disorder*) AND depression))

Search #2: Diabetes mellitus

(exp Diabetes Mellitus/) OR

(diabet* OR NIDDM OR IDDM OR T2D* OR T1D*) OR

("non-insulin* depend*" OR "noninsulin* depend*" OR "insulin* depend*")

Search #3: pharmacological interventions for diabetes

(exp Drug Therapy/ OR exp Pharmacology/ OR exp Psychopharmacology/ OR exp Metabolic Side Effects of Drugs and Substances/ OR exp Pharmacologic Actions/ OR exp Drug Effects/ OR exp Psychotropic Drugs/) OR

((drug* OR pharmac* OR medic* OR psychotrop*) AND (intervent* OR therap* OR treat* OR care OR service)) OR (drug* OR medic*) OR

((glucose* OR glycaem*) AND (treat* OR control* OR care OR servic* OR therap* OR interven* OR manag* OR monit*)) OR

(metformin OR sulphonylureas OR insulin OR thiazolidinediones) OR

((switch* AND (medic* OR drug*)) OR "appetite suppressant*" OR antiparkinsonian OR anticonvulsant* OR antidepressant* OR "health check*") OR

(weight AND (loss OR reduc* OR maint*)) OR ("weight gain" AND (prevent* OR manag*)) OR

((smok* OR tobacco OR nicotin* OR cigarette*) AND (cessation OR reduc* OR abst*))

For people with SMD and diabetes mellitus, what non-pharmacological interventions are effective to improve glycaemic control?

Search #1: SMD

(exp Mental Disorders/ OR exp Psychotic Disorders/ OR exp Bipolar and Related Disorders/ OR exp Depressive Disorder) OR

((Mental AND (disorder* OR disabilit* OR illness OR "health condition" OR "health problem" OR distress)) OR "psychological distress" OR "psychiatric disorder") OR

((schizophrenia OR schizophrenic) OR Schizotyp* OR ((Delusional OR paranoid) AND disorder*) OR hallucination* OR Psychotic OR Schizoaffective OR psychosis) OR

(((manic OR bipolar OR mood) AND disorder*) OR (depressive AND (disorder* OR episode*)) OR "depressive symptom*" OR hypomania OR mania* OR ((major OR psychotic OR disorder*) AND depression))

Search #2: Diabetes mellitus

(exp Diabetes Mellitus/) OR

(diabet* OR NIDDM OR IDDM OR T2D* OR T1D*) OR

("non-insulin* depend*" OR "noninsulin* depend*" OR "insulin* depend*")

Search #3: non-pharmacological interventions for diabetes

(exp Diet, Diabetic/) OR

(exp Exercise Therapy/ OR exp Occupational Therapy/ OR exp Therapy/ OR exp Therapeutics/ OR exp Family Therapy/ OR exp Psychotherapy/ OR exp Cognitive Therapy/ OR exp Behaviour Therapy/ OR exp Counseling/ OR exp Mental Health Services/ OR exp Problem Based Learning/ OR exp Problem Solving/) OR

((psychosocial OR psycho* OR lifestyle* OR cognit* OR behaviour* OR behaviour* OR non-pharmac* OR organisat* OR organizat*) AND (intervent* OR therap* OR treat* OR care OR servic*)) OR

("problem solving" OR psychoeducation OR couns* OR education) OR

((glucose* OR glycaem*) AND (treat* OR control* OR care OR servic* OR therap* OR interven* OR manag* OR monit*)) OR

(diet* OR nutrition* OR exercis* OR "physical activity" OR "health promot*" OR self-monit* OR self-manag* OR self-care OR calor* OR "healthy eating" OR "healthy body weight" OR "food intake" OR "health check*") OR

(weight AND (loss OR reduc* OR maint*)) OR ("weight gain" AND (prevent* OR manag*)) OR

((smok* OR tobacco OR nicotin* OR cigarette*) AND (cessation OR reduc* OR abst*))

PICO QUESTION 7

For people with SMD and HIV/AIDS, what pharmacological interventions (i.e. ART drugs) and non-pharmacological interventions are effective to support reduction in HIV-related outcomes?

Search #1: SMD

(exp Mental Disorders/ OR exp Psychotic Disorders/ OR exp Bipolar and Related Disorders/ OR exp Depressive Disorder) OR

((Mental AND (disorder* OR disabilit* OR illness OR "health condition" OR "health problem" OR distress)) OR "psychological distress" OR "psychiatric disorder") OR

((schizophrenia OR schizophrenic) OR Schizotyp* OR ((Delusional OR paranoid) AND disorder*) OR hallucination* OR Psychotic OR Schizoaffective OR psychosis) OR

(((manic OR bipolar OR mood) AND disorder*) OR (depressive AND (disorder* OR episode*)) OR "depressive symptom*" OR hypomania OR mania* OR ((major OR psychotic OR disorder*) AND depression))

Search #2: HIV/AIDS

(exp HIV/ OR exp Sexually Transmitted Diseases/ OR exp Lymphoma, AIDS-Related/ OR exp HIV Long-Term Survivors/ OR exp HIV Infections OR exp Acquired Immunodeficiency Syndrome/) OR

(HIV OR "human immunodeficiency syndrome" OR "human immunodeficiency virus" OR AIDS OR "acquired immunodeficiency syndrome")

Search #3: interventions for HIV/AIDS

(exp HIV Antigens/ OR exp Anti-HIV Agents/ OR exp Anti-Retroviral Agents/ OR exp Antiretroviral Therapy, Highly Active/ OR exp AIDS Vaccines/) OR

(exp Drug Therapy/ OR exp Pharmacology/ OR exp Psychopharmacology/ OR exp Metabolic Side Effects of Drugs and Substances/ OR exp Pharmacologic Actions/ OR exp Drug Effects/ OR exp Psychotropic Drugs/) OR

((drug* OR pharmac* OR medic* OR psychotrop*) AND (intervent* OR therap* OR treat* OR care OR servic)) OR (drug* OR medic*) OR

((“anti-retroviral” OR ART) AND (drug* OR medic* OR intervent* OR therap* OR treat* OR care)) OR

(tenofovir OR TDF OR lamivudine OR 3TC OR emtricitabine OR FTC OR efavirenz OR EFV OR Abacavir

OR Zidovudine OR Nevirapine OR Atazanavir OR ritonavir OR Darunavir OR Lopinavir OR Dolutegravir OR Raltegravir)

PICO QUESTION 8

For people with SMD and infectious diseases (Tuberculosis, Hepatitis B/C), what pharmacological and non-pharmacological interventions are effective for treatment of infectious diseases (e.g. tuberculosis, hepatitis B, hepatitis C)?

Search #1: SMD

(exp Mental Disorders/ OR exp Psychotic Disorders/ OR exp Bipolar and Related Disorders/ OR exp Depressive Disorder) OR

((Mental AND (disorder* OR disabilit* OR illness OR “health condition” OR “health problem” OR distress)) OR "psychological distress" OR "psychiatric disorder") OR

((schizophrenia OR schizophrenic) OR Schizotyp* OR ((Delusional OR paranoid) AND disorder*) OR hallucination* OR Psychotic OR Schizoaffective OR psychosis) OR

(((manic OR bipolar OR mood) AND disorder*) OR (depressive AND (disorder* OR episode*)) OR "depressive symptom*" OR hypomania OR mania* OR ((major OR psychotic OR disorder*) AND depression))

Search #2: infectious diseases (tuberculosis, hepatitis B/C)

(exp Hepatitis/ OR exp Hepatitis, Viral, Human/ OR exp Tuberculosis/ OR exp Hepatitis B/ OR exp Hepatitis B Virus/ OR exp Hepatitis C/) OR

(“hepatitis B” OR “hepatitis C” OR tuberculosis)

Search #3: interventions for infectious diseases

(exp Hepatitis B Vaccines/ OR exp Hepatitis B Antigens/ OR exp Hepatitis C Antigens/ OR exp Tuberculosis Vaccines/) OR

(exp Drug Therapy/ OR exp Pharmacology/ OR exp Psychopharmacology/ OR exp Metabolic Side Effects of Drugs and Substances/ OR exp Pharmacologic Actions/ OR exp Drug Effects/ OR exp Psychotropic Drugs/) OR

((drug* OR pharmac* OR medic* OR psychotrop*) AND (intervent* OR therap* OR treat* OR care OR servic)) OR (drug* OR medic*) OR

(vaccin* OR BCG OR treatment adherence OR treatment completion) OR

(Ethambutol OR Rifampicin OR Insoniazid OR Pyrazinamide OR Rifabutin OR Rifampicin OR Rifapentine OR Entecavir OR Tenofovir OR Sofosbuvir OR Simeprevir OR Daclatasvir OR Dasabuvir OR Ribavarin OR Pegylated interferon)

Drug-drug interactions search strategy

Drug-drug interaction searches were conducted between medicines relevant for each PICO question and medicines used for SMD. The following process was employed for the searches:

Medicines of interest were identified for each PICO question by referring to relevant sections of the 2017 WHO Model List of Essential Medicines (EML), as well as prior WHO Guidelines and WHO Mental Health Gap Action Programme Intervention Guide (mhGAP-IG) where applicable. Physical health medicines were limited in scope to those used on a routine basis, rather than emergently. Technical consultation was also sought with relevant departments of WHO. Pharmacological interventions recommended in the forthcoming guidelines were also included.

Medicines used for SMD were limited to those included in the WHO mhGAP-IG and/or the 2017 WHO EML. These will be expanded to include a wider range of medicines which may be used in different settings based on availability and costs. Since its inception in 1977, the WHO Model List of Essential Medicines has played an important role in identifying priority medications for major health conditions in countries of all income groups. Updated every two years, this list in many cases has been used as a gold standard for national health systems and non-governmental organization. Priority medications are selected based on efficacy, safety, and cost-effectiveness.

Searches between both lists (medicines relevant for each PICO question and medicines used for SMD) were run using the drug-drug interaction software Lexi-Interact. Lexi-Interact was chosen as it is commonly used in clinical practice and scored well on accuracy and comprehensiveness in a recent review comparing 5 drug-drug interaction engines[5]. Severity of drug-drug interactions (minor, moderate, major)) were reported in the Lexi-Interact database and have reported here.

Search results for each PICO question were summarized into a narrative synthesis within each Evidence Profile, as well as a table coded by drug-drug interaction severity with accompanying information in the annex.

[2] Sh Kheshti R, Aalipour M, Namazi S. "A comparison of five common drug-drug interaction software programs regarding accuracy and comprehensiveness." Journal of Research in Pharmacy Practice. 2016; 5: 257-263.

Annex 6. Drug – drug interactions

PICO 2: TOBACCO CESSATION

[The following table and information is summarized from drug-drug interaction searches using Lexi-Interact.]

- No interaction known or minor interaction
- Moderate interaction
- Major interaction

	Amitriptyline	Fluoxetine	Haloperidol	Risperidone	Chlorpromazine	Fluphenazine	Clozapine	Biperiden	Trihexyphenidyl	Lithium	Valproic acid	Carbamazepine	Diazepam
Bupropion	🟡	🟡	🟡	🟡	🟡	🟡	🟡	🟢	🟢	🟢	🟢	🟡	🟢
Varenicline	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟢
NRT	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟢

There are no known interactions between **NRT** or **varenicline** and medicines used for SMD.

BUPROPION:
There are multiple interactions between bupropion and medicines used for SMD, specifically involving elevated seizure risk and enzymatic inhibition/induction.

- **Amitriptyline:** Moderate interaction [elevated amitriptyline levels via CYP2D6 inhibition]. ADVICE: Consider other medications. If using, monitor clinically for signs of amitriptyline toxicity.
- **Fluoxetine:** Moderate interaction [elevated fluoxetine levels via CYP2D6 inhibition]. ADVICE: Monitor clinically for signs of fluoxetine toxicity and/or serotonin syndrome.
- **Haloperidol, risperidone, chlorpromazine, fluphenazine:** Moderate interaction [decreased seizure threshold]. Advise caution.
- **Clozapine:** Moderate interaction [decreased seizure threshold, elevated clozapine levels via CYP2D6 inhibition]. ADVICE: Monitor for signs of clozapine toxicity clinically and via testing of levels. Adjust clozapine dose accordingly.
- **Carbamazepine (CBZ):** Moderate interaction [lower levels of bupropion via CYP2B6 induction]. ADVICE: Monitor for clinical efficacy of bupropion.

PICO 3: WEIGHT MANAGEMENT

[The following table and information is summarized from drug-drug interaction searches using Lexi-Interact.]

- No interaction known or minor interaction
- Moderate interaction
- Major interaction

	Amitriptyline	Fluoxetine	Haloperidol	Risperidone	Chlorpromazine	Fluphenazine	Clozapine	Biperiden	Trihexyphenidyl	Lithium	Valproic acid	Carbamazepine	Diazepam
Metformin	●	●	●	●	●	●	●	●	●	●	●	●	●

METFORMIN:

- **Fluoxetine:** Moderate interaction [increased potency of anti-diabetic medicine]. ADVICE: Monitor blood glucose control and adjust dosing of anti-diabetic medicine.

- **Risperidone, Clozapine:** Moderate interaction [decreased efficacy of anti-diabetic medicine]. ADVICE: Monitor glycemic control and adjust dosing of anti-diabetic medicine.

PICO 4: SUBSTANCE USE DISORDERS

[The following table and information is summarized from drug-drug interaction searches using Lexi-Interact.]

- No interaction known or minor interaction
- Moderate interaction
- Major interaction

	Amitriptyline	Fluoxetine	Haloperidol	Risperidone	Chlorpromazine	Fluphenazine	Clozapine	Biperiden	Trihexyphenidyl	Lithium	Valproic acid	Carbamazepine	Diazepam
Methadone	🔴	🔴	🔴	🔴	🔴	🔴	🔴	🟡	🟡	🔴	🟢	🟡	🔴
Buprenorphine	🔴	🔴	🔴	🔴	🔴	🔴	🔴	🟡	🟡	🔴	🟢	🔴	🔴

METHADONE:
There are multiple interactions between methadone and medicines for SMD, including increased risk for CNS depression* (sedation, confusion, decreased respiratory drive), QT-prolongation (methadone carries moderate risk), and serotonergic effects. Signs of serotonin syndrome include confusion, neuromuscular excitability, and dysautonomia.

- **Biperiden, trihexyphenidyl:** Moderate interaction. Elevated risk of side effects and toxicity of methadone including urinary retention and constipation [via anticholinergic activity]. ADVICE: Monitor for side effects.
- **Carbamazepine (CBZ):** Moderate interaction [reduced methadone levels and efficacy via CYP3A4 induction]. ADVICE: If using, monitor for reduced efficacy of methadone or opioid withdrawal symptoms.
- **Amitriptyline:** Major interaction [risk of CNS depression, serotonergic effects]. ADVICE: Avoid concurrent use if possible. If using, use lowest doses possible; monitor for clinical signs of CNS depression and signs of serotonin syndrome. Stop both medicines if serotonin syndrome suspected.
- **Fluoxetine:** Major interaction [high risk of QT prolongation, serotonergic effects]. ADVICE: Avoid using.
- **Haloperidol, risperidone, chlorpromazine, clozapine:** Major interaction [risk of CNS depression, risk of QT prolongation]. ADVICE: Avoid using if possible. If using, use lowest doses possible; monitor for clinical signs of CNS depression; monitor for QT-prolongation and arrhythmias on ECG.
- **Fluphenazine:** Major interaction [risk of CNS depression]. ADVICE: Avoid using if possible. If using, use lowest doses possible and monitor for clinical signs of CNS depression.
- **Lithium:** Major interaction [serotonergic effects], Moderate interaction [risk of QT prolongation]. ADVICE: If using, monitor clinically for signs of serotonin syndrome. Stop both medicines if serotonin syndrome is suspected. Additionally, monitor for QT prolongation and arrhythmias on ECG if possible.
- **Diazepam:** Major interaction [risk of CNS depression]. ADVICE: Avoid using if possible. If using, monitor for clinical signs of CNS depression.

BUPRENORPHINE:
There are multiple interactions between buprenorphine and medicines for SMD, including increased risk for CNS depression* (sedation, confusion, decreased respiratory drive), QT prolongation, and serotonergic effects (bupropion can increase the risk of serotonin toxicity or serotonin syndrome if used with medicines that have serotonergic effects). Signs of serotonin syndrome include confusion, neuromuscular excitability, and dysautonomia.

- **Biperiden, trihexyphenidyl:** Moderate interaction. Elevated risk of side effects and toxicity of buprenorphine including urinary retention and constipation [via anticholinergic activity]. ADVICE: Monitor for side effects.

- **Amitriptyline:** Major interaction [risk of CNS depression, serotonergic effects]. ADVICE: If using, consider decreasing amitriptyline and starting buprenorphine at a low dose; monitor for clinical signs of CNS depression. Additionally, monitor clinically for signs of serotonin syndrome. Stop both medicines if this syndrome is suspected.

- **Fluoxetine:** Major interaction [serotonergic effects], Moderate interaction [risk of QT prolongation]. Fluoxetine confers high-risk for QT interval prolongation and buprenorphine may increase this risk, though the evidence is unclear. ADVICE: monitor clinically for signs of serotonin syndrome. Stop both medicines if this syndrome is suspected. Monitor ECG if possible.

- **Haloperidol, risperidone, chlorpromazine, fluphenazine, clozapine, carbamazepine, diazepam:** Major interaction [risk of CNS depression]. ADVICE: Avoid using if concerns for risk of buprenorphine misuse. If using, consider decreasing other sedating medicines and starting buprenorphine at a low dose; monitor for clinical signs of CNS depression.

- **Lithium:** Major interaction [serotonergic effects]. ADVICE: Monitor clinically for signs of serotonin syndrome. Stop both medicines if this syndrome is suspected.

* Of note, the US FDA issued a safety announcement in 2017 regarding the use of methadone and buprenorphine with other sedating medications. While the risks of CNS sedation can be serious, they may be outweighed by the risk of other harms of untreated opioid use disorders. Thus, the US FDA does not recommend withholding opioid replacement therapy in the context of other sedating medications; cautious medication management is advised. United States Food and Drug Administration. Drug Safety and Availability - FDA Drug Safety Communication: FDA urges caution about withholding opioid addiction medications from patients taking benzodiazepines or CNS depressants: careful medication management can reduce risks. 2017. https://www.fda.gov/Drugs/DrugSafety/ucm575307.htm

PICO 5: CARDIOVASCULAR DISEASE

[The following table and information is summarized from drug-drug interaction searches using Lexi-Interact.]

- No interaction known or minor interaction
- Moderate interaction
- Major interaction

	Amitriptyline	Fluoxetine	Haloperidol	Risperidone	Chlorpromazine	Fluphenazine	Clozapine	Biperiden	Trihexyphenidyl	Lithium	Valproic acid	Carbamazepine	Diazepam
Bisoprolol	●	●	●	●	●	●	●	●	●	●	●	●	●
Atenolol	●	●	●	●	●	●	●	●	●	●	●	●	●
Metoprolol	●	●	●	●	●	●	●	●	●	●	●	●	●
Carvedilol	●	●	●	●	●	●	●	●	●	●	●	●	●
Glyceryl trinitrate	●	●	●	●	●	●	●	●	●	●	●	●	●
Isosorbide dinitrate	●	●	●	●	●	●	●	●	●	●	●	●	●
Verapamil	●	●	●	●	●	●	●	●	●	●	●	●	●
Digoxin	●	●	●	●	●	●	●	●	●	●	●	●	●
Amiodarone	●	●	●	●	●	●	●	●	●	●	●	●	●
Amlodipine	●	●	●	●	●	●	●	●	●	●	●	●	●
Enalapril	●	●	●	●	●	●	●	●	●	●	●	●	●
Hydrochlorothiazide	●	●	●	●	●	●	●	●	●	●	●	●	●
Losartan	●	●	●	●	●	●	●	●	●	●	●	●	●
Furosemide	●	●	●	●	●	●	●	●	●	●	●	●	●
Spironolactone	●	●	●	●	●	●	●	●	●	●	●	●	●
Aspirin	●	●	●	●	●	●	●	●	●	●	●	●	●
Clopidogrel	●	●	●	●	●	●	●	●	●	●	●	●	●
Simvastatin	●	●	●	●	●	●	●	●	●	●	●	●	●
Metformin	●	●	●	●	●	●	●	●	●	●	●	●	●

There are no known interactions between digoxin and medicines used for SMD.

BETA-BLOCKERS:

As a class, beta-blockers have significant interactions with multiple SMD medicines, most significantly the risk of hypotension or beta-blocker toxicity (including hypotension, bradycardia, and heart block/prolonged PR interval). There are some variations within this class.

- **Risperidone, chlorpromazine, fluphenazine, clozapine:** Moderate interaction for most beta-blockers [risk of hypotension] ADVICE: Monitor therapy.
- **Fluoxetine (with carvedilol and metoprolol only):** Moderate interaction with carvedilol, Major interaction with metoprolol. [Elevated levels of beta blocker via CYP2D6 inhibition] ADVICE: Consider alternative. If using, monitor for signs of beta blocker toxicity; adjust dosing accordingly.
- **Carbamazepine (with bisoprolol only):** Major interaction [reduced levels and efficacy of bisoprolol via CYP3A4 induction]. ADVICE: Consider alternative. If using, monitor for reduced efficacy of bisoprolol.

GLYCERYL TRINITRATE:

- **Amitriptyline, haloperidol, risperidone, chlorpromazine, fluphenazine, clozapine, biperiden, trihexyphenidyl:** Moderate interaction [reduced absorption of sublingual glyceryl trinitrate due to dry mouth from anticholinergic effects]. ADVICE: If dry mouth develops, utilize strategies such as artificial saliva and chewing gum

ISOSORBIDE DINITRATE:

- **Risperidone, chlorpromazine, clozapine:** Moderate interaction [elevated risk of hypotension] ADVISE caution and monitor.
- **Carbamazepine:** Major interaction [reduced levels and efficacy of isosorbide dinitrate] ADVICE: Consider alternative.

VERAPAMIL:

Verapamil may elevate the levels of multiple medicines due to P-glycoprotein, CYP3A4, or CYP1A2 inhibition.

- **Haloperidol, risperidone, clozapine:** Moderate interaction [elevated levels of antipsychotic via CYP3A4, P-glyocoprotein, or CYP1A2 inhibition] ADVICE: Monitor for toxicity of antipsychotic
- **Chlorpromazine:** Moderate interaction [elevated risk of hypotension] ADVICE: Monitor blood pressure and adjust doses accordingly
- **Lithium:** Moderate interaction [increased risk of neurotoxicity from lithium; unclear effect on levels] ADVICE: Monitor clinically, as well as via laboratory levels
- **Diazepam:** Moderate interaction [increased levels of diazepam via CYP3A4 inhibition] ADVICE: Monitor for signs of diazepam toxicity
- **Carbamazepine (CBZ):** Major interaction [reduced levels and efficacy of verapamil via CYP3A4 induction, elevated levels of CBZ via CYP3A4 inhibition] ADVICE: Consider another mood stabilizer

AMIODARONE:

- **Fluoxetine, haloperidol, risperidone, chlorpromazine, clozapine:** Major interaction [QT prolongation] ADVICE: Avoid using
- **Amitriptyline, lithium:** Major interaction [QT prolongation] ADVICE: If able, avoid using. If using, monitor for QT-prolongation and arrythmias on ECG.
- **Carbamazepine:** Major interaction [reduced levels and efficacy of amiodarone] ADVICE: Consider another mood stabilizer. If using, monitor for reduced efficacy of amiodarone.

AMLODIPINE:

- **Risperidone, chlorpromazine, clozapine:** Moderate interaction [risk of hypotension] ADVICE: Monitor blood pressure and adjust doses accordingly
- **Carbamazepine:** Major interaction [reduced levels and efficacy of amlodipine via CYP3A4 induction] ADVICE: Consider another mood stabilizer. If using, monitor for reduced efficacy of amlodipine and adjust doses accordingly.

ENALAPRIL, LOSARTAN:

- **Risperidone, chlorpromazine, clozapine:** Moderate interaction [risk of hypotension] ADVICE: Monitor blood pressure and adjust doses accordingly
- **Lithium:** Moderate interaction with losartan, Major interaction with enalapril. [Elevated levels of lithium] ADVICE: Consider decreasing lithium when starting losartan or enalapril. Monitor for signs of lithium toxicity clinically and via laboratory testing.
- **Carbamazepine (with losartan only):** Major interaction [reduced levels and efficacy of losartan via CYP3A4 induction] ADVICE: Consider another mood stabilizer. If used, monitor for reduced efficacy of losartan.

DIURETICS (HCTZ, FUROSEMIDE, SPIRONOLACTONE):

Diuretics have significant interactions with multiple SMD medicines, including the risk of hypotension.

- **Risperidone, chlorpromazine, clozapine:** Moderate interaction [risk of hypotension] ADVICE: Monitor blood pressure and adjust doses accordingly
- **Amitriptyline, haloperidol, fluphenazine, biperiden, trihexyphenidyl, risperidone, chlorpromazine, clozapine (with HCTZ only):** Moderate interaction [increased levels of HCTZ due to effects on gut motility] ADVICE: Monitor for side effects of HCTZ
- **Fluoxetine, carbamazepine (with HCTZ only):** Moderate interaction [increased risk of hyponatremia] ADVICE: Monitor for clinical signs of hyponatremia including headache, dizziness, nausea, confusion, seizures
- **Lithium (with HCTZ only):** Moderate interaction [increased lithium levels] ADVICE: Consider decreasing lithium dose when HCTZ is started. Monitor for signs of lithium toxicity clinically and via laboratory testing.
- **Risperidone with furosemide only:** Major interaction [increased risk of mortality in patients with dementia] ADVICE: Consider another antipsychotic. If using, monitor carefully, especially hydration status.

ASPIRIN:

- **Amitriptyline, fluoxetine:** Major interaction [increased risk of bleeding, especially gastrointestinal bleeding] ADVICE: Monitor for signs of bleeding
- **Valproic acid:** [VPA] Moderate interaction [elevated levels of VPA] ADVICE: Monitor for toxicity of VPA clinically and via laboratory testing if possible

CLOPIDOGREL:

- **Fluoxetine:** Major interaction [reduced levels of active metabolite of clopidogrel via CYP2C19 inhibition] ADVICE: Consider another antidepressant. If using, monitor for reduced efficacy of clopidogrel.

SIMVASTATIN:

- **Risperidone:** Moderate interaction [increased risk of myopathy and rhabdomyolysis] ADVICE: Monitor clinically for any concerning symptoms
- **Carbamazepine:** Major interaction [reduced levels and efficacy of simvastatin via CYP3A4 induction] ADVICE: Consider another mood stabilizer. If using, monitor for reduced efficacy of simvastatin.

METFORMIN:

- **Fluoxetine:** Moderate interaction [increased potency of anti-diabetic medicine]. ADVICE: Monitor blood glucose control and adjust dosing of anti-diabetic medicine.
- **Risperidone, Clozapine:** Moderate interaction [decreased efficacy of anti-diabetic medicine]. ADVICE: Monitor glycaemic control and adjust dosing of anti-diabetic medicine.

PICO 6: DIABETES

[The following table and information is summarized from drug-drug interaction searches using Lexi-Interact.]

- No interaction known or minor interaction
- Moderate interaction
- Major interaction

	Amitriptyline	Fluoxetine	Haloperidol	Risperidone	Chlorpromazine	Fluphenazine	Clozapine	Biperiden	Trihexyphenidyl	Lithium	Valproic acid	Carbamazepine	Diazepam
Metformin	●	●	●	●	●	●	●	●	●	●	●	●	●
Gliclazide	●	●	●	●	●	●	●	●	●	●	●	●	●
Insulin	●	●	●	●	●	●	●	●	●	●	●	●	●

METFORMIN, INSULIN:

- **Fluoxetine:** Moderate interaction [increased potency of anti-diabetic medicine]. ADVICE: Monitor blood glucose control and adjust dosing of anti-diabetic medicine.
- **Risperidone, Clozapine:** Moderate interaction [decreased efficacy of anti-diabetic medicine]. ADVICE: Monitor glycaemic control and adjust dosing of anti-diabetic medicine.

GLICLAZIDE:

- **Amitriptyline, Fluoxetine:** Moderate interaction [increased potency of anti-diabetic medicine]. ADVICE: Monitor blood glucose control and adjust dosing of anti-diabetic medicine.
- **Risperidone, Clozapine:** Moderate interaction [decreased efficacy of anti-diabetic medicine]. ADVICE: Monitor glycaemic control and adjust dosing of anti-diabetic medicine.

PICO 7: HIV/AIDS

[The following table and information is summarized from drug-drug interaction searches using Lexi-Interact.]

- No interaction known or minor interaction
- Moderate interaction
- Major interaction

	Amitriptyline	Fluoxetine	Haloperidol	Risperidone	Chlorpromazine	Fluphenazine	Clozapine	Biperiden	Trihexyphenidyl	Lithium	Valproic acid	Carbamazepine	Diazepam
Dolutegravir	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🔴	🟢
Efavirenz	🟡	🔴	🔴	🔴	🔴	🟡	🔴	🟢	🟢	🟡	🟢	🔴	🟡
Emtricitabine	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟢
Lamivudine	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟢
Tenofovir disoproxil fumarate (TDF)	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟢

There are no known interactions between **emtricitabine, lamivudine**, or **tenofovir disoproxil fumarate (TDF)** and medicines used for SMD.

DOLUTEGRAVIR (DTG):

Major interaction with carbamazepine (CBZ).

- **CBZ** may reduce the level and efficacy of DTG. ADVICE: Double the dose of DTG if patient not on integrase inhibitors before. If resistance suspected to DTG (or similar drug in the same class), choose another mood stabilizer.

EFAVIRENZ:

There are multiple interactions between Efavirenz and medicines used for SMD, specifically involving the risk of QT interval prolongation, the risk of CNS depression (ex: sedation, confusion, decreased respiratory drive), and/or enzymatic induction.

- **Amitriptyline:** Moderate interaction [QT prolongation, risk of CNS depression]. ADVICE: If using, monitor for QT-prolongation and arrhythmias on ECG if possible and monitor for signs of CNS depression.
- **Lithium:** Moderate interaction [QT prolongation]. ADVICE: If using, monitor for QT-prolongation and arrhythmias on ECG if possible
- **Fluphenazine, Diazepam:** Moderate interaction [risk of CNS depression]. ADVICE: If using, monitor for signs of CNS depression.
- **Haloperidol, risperidone, chlorpromazine, and clozapine:** Major interaction [QT prolongation]. ADVICE: If able, avoid using efavirenz with these medicines. If using, monitor for QT-prolongation and arrythmias on ECG.
- **Fluoxetine:** Major interaction [high risk of QT prolongation]. ADVICE: Avoid using.
- **Carbamazepine:** Major interaction. Efavirenz and carbamazepine may reduce the levels (and efficacy) of each other. ADVICE: Avoid using.

* For details as to interactions between second-line and third-line antiretroviral and psychiatric medicines, please refer to (Annex 13: Key drug-drug interactions for antiretroviral drugs), which is available online at the following link: http://apps.who.int/iris/bitstream/handle/10665/208825/9789241549684_eng.pdf?sequence=1

PICO 8: TUBERCULOSIS

[The following table and information is summarized from drug-drug interaction searches using Lexi-Interact.]

- No interaction known or minor interaction
- Moderate interaction
- Major interaction

	Amitriptyline	Fluoxetine	Haloperidol	Risperidone	Chlorpromazine	Fluphenazine	Clozapine	Biperiden	Trihexyphenidyl	Lithium	Valproic acid	Carbamazepine	Diazepam
Isoniazid	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟡	🟡	🟢
Rifampin/ Rifampicin	🟡	🟡	🔴	🟡	🟢	🟢	🔴	🟢	🟢	🟢	🔴	🔴	🔴
Pyrazinamide	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟢
Ethambutol	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟢
Levofloxacin	🟡	🟡	🔴	🔴	🔴	🟢	🔴	🟢	🟢	🟡	🟢	🟢	🟢
Cycloserine	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟢
Bedaquiline	🟡	🟡	🔴	🔴	🔴	🟢	🔴	🟢	🟢	🟡	🟢	🔴	🟢
Delamanid	🟡	🟡	🔴	🔴	🔴	🟢	🔴	🟢	🟢	🟡	🟢	🔴	🟢
Linezolid	🔴	🔴	🟡	🟡	🟡	🟡	🟡	🟢	🟢	🔴	🟢	🔴	🟢

There are no known interactions between pyrazinamide, ethambutol, or cycloserine and medicines used for SMD.

ISONIAZID (INH):

- **Valproic acid:** Moderate interaction. INH can increase valproic acid levels. ADVICE: If using, monitor for valproic acid toxicity clinically and via laboratory testing of levels, if possible, especially when starting, stopping, or adjusting INH.
- **Carbamazepine (CBZ):** Moderate interaction. INH can increase CBZ levels and CBZ may increase the hepatotoxicity of INH. ADVICE: If using, monitor for clinical signs of CBZ toxicity and hepatotoxicity.

RIFAMPIN/RIFAMPICIN:

There are multiple interactions between rifampin and medicines used for SMD due to rifampin's ability to induce multiple enzymes (rifampin is a strong inducer of CYP3A4 and CYP2C9).

- **Amitriptyline:** Moderate interaction [reduced levels and efficacy of amitriptyline]. ADVICE: Monitor clinically for efficacy of amitriptyline.
- **Fluoxetine:** Moderate interaction [reduced levels and efficacy of fluoxetine]. Mechanism: CYP2C9 induction. ADVICE: Monitor clinically for efficacy of fluoxetine.
- **Risperidone:** Moderate interaction [reduced levels and efficacy of risperidone]. Mechanism: CYP3A4 induction. ADVICE: Monitor clinically for efficacy of risperidone and adjust dosing accordingly.
- **Haloperidol:** Major interaction [reduced levels and efficacy of haloperidol]. Mechanism: CYP3A4 induction. ADVICE: Consider another antipsychotic medication. If using, monitor for clinical efficacy of haloperidol and adjust dosing as needed.

- **Clozapine:** Major interaction [reduced levels and efficacy of clozapine]. Mechanism: CYP3A4 induction. ADVICE: Avoid using. If using, monitor for efficacy clinically and via clozapine levels and adjust dosing as needed.
- **Valproic acid (VPA):** Major interaction [reduced levels and efficacy of VPA]. ADVICE: Monitor for efficacy clinically and via VPA levels if possible, especially with dosing changes of rifampin; adjust VPA dosing accordingly.
- **Carbamazepine (CBZ):** Major interaction [reduced levels and efficacy of carbamazepine]. Mechanism: CYP3A4 induction. ADVICE: Consider another mood stabilizer. If using, monitor for clinical efficacy of CBZ and adjust dosing as needed.
- **Diazepam:** Major interaction [reduced levels and efficacy of diazepam]. Mechanism: CYP2C19 and CYP3A4 induction. ADVICE: Consider another medicine. If using, monitor for clinical efficacy of diazepam and adjust dosing as needed.

LEVOFLOXACIN:

There are multiple interactions between levofloxacin and medicines used for SMD due to increased risk for QT-prolongation (levofloxacin confers moderate risk).

- **Amitriptyline, fluoxetine, lithium:** Moderate interaction [increased risk for QT-prolongation]. ADVICE: Monitor for QT-prolongation and arrhythmias by ECG.
- **Haloperidol, risperidone, chlorpromazine, clozapine:** Major interaction [risk of QT prolongation]. ADVICE: Avoid using if possible. If using, monitor for QT-prolongation and arrhythmias on ECG.

BEDAQUILINE & DELAMANID:

There are multiple interactions between bedaquiline and delamanid with medicines used for SMD due to increased risk for QT-prolongation (both bedaquiline and delamanid confer moderate risk) and induction by CYP3A4.

- **Amitriptyline, fluoxetine, lithium:** Moderate interaction [increased risk for QT-prolongation]. ADVICE: Monitor for QT-prolongation and arrhythmias by ECG.
- **Haloperidol, risperidone, chlorpromazine, clozapine:** Major interaction [risk of QT prolongation]. ADVICE: Avoid using if possible. If using, monitor for QT-prolongation and arrhythmias on ECG.
- **Carbamazepine (CBZ):** Major interaction [reduced levels and effectiveness of bedaquiline or delamanid]. ADVICE: Consider another mood stabilizer.

LINEZOLID:

There are multiple interactions between linezolid and medicines used for SMD due to serotonergic effects, dopamine antagonism, and monoamine oxidase inhibition. Signs of serotonin syndrome include confusion, neuromuscular excitability (ex: myoclonus and hyperreflexia), and dysautonomia (ex: flushing, sweating, diarrhoea, high blood pressure and heart rate, and fever). Signs of neuroleptic malignant syndrome include confusion, muscle rigidity, and dysautonomia (ex: high fever, heart rate, or labile blood pressures).

- **Amitriptyline:** Major interaction [serotonergic effects, risk of serotonin syndrome]. ADVICE: Do not use concurrently. Stop amitriptyline at least two weeks before starting linezolid. If linezolid is necessary in an emergency situation, stop amitriptyline and monitor clinically for signs of serotonin syndrome for at least two weeks after amitriptyline is stopped (while linezolid treatment is ongoing) or until one day after linezolid is stopped.
- **Fluoxetine:** Major interaction [serotonergic effects, risk of serotonin syndrome]. ADVICE: Do not use concurrently. Stop fluoxetine at least five weeks before starting linezolid. If linezolid is necessary in an emergency situation, stop fluoxetine and monitor clinically for signs of serotonin syndrome for at least five weeks after fluoxetine is stopped (while linezolid treatment is ongoing) or until one day after linezolid is stopped.
- **Haloperidol, risperidone, chlorpromazine, fluphenazine:** Moderate interaction [serotonergic effects and dopamine antagonism, risk of serotonin syndrome and neuroleptic malignant syndrome]. ADVICE: Monitor clinically for signs of serotonin syndrome and neuroleptic malignant syndrome.
- **Clozapine:** Moderate interaction [serotonergic effects, dopamine antagonism, myelosuppressive effects, risk of serotonin syndrome and neuroleptic malignant syndrome, risk of neutropenia]. ADVICE: Monitor clinically for signs of serotonin syndrome and neuroleptic malignant syndrome. Monitor neutrophil count closely.
- **Lithium:** Major interaction [serotonergic effects, risk of serotonin syndrome]. ADVICE: Do not use concurrently. Stop lithium at least two weeks before starting linezolid. If linezolid is necessary in an emergency situation, stop lithium and monitor clinically for signs of serotonin syndrome for at least two weeks after lithium is stopped (while linezolid treatment is ongoing) or until one day after linezolid is stopped.
- **Carbamazepine:** Major interaction [risk of increased monoamine oxidase inhibition by linezolid]. ADVICE: Do not use concurrently. Do not use carbamazepine for two weeks after stopping linezolid.

PICO 8: HEPATITIS B/C

[The following table and information is summarized from drug-drug interaction searches using Lexi-Interact.]

- No interaction known or minor interaction
- Moderate interaction
- Major interaction

	Amitriptyline	Fluoxetine	Haloperidol	Risperidone	Chlorpromazine	Fluphenazine	Clozapine	Biperiden	Trihexyphenidyl	Lithium	Valproic acid	Carbamazepine	Diazepam
Tenofovir	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟢
Entecavir	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟢
Sofosbuvir	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🔴	🟢
Daclatasvir	🟢	🟢	🟢	🟡	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🔴	🟢
Ribavirin	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟢
Ledipasvir	🟢	🟢	🟢	🟡	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🔴	🟢

There are no known interactions between **tenofovir**, **entecavir**, or **ribavirin** and medicines used for SMD.

SOFOSBUVIR:

- **Carbamazepine (CBZ):** Major interaction. Levels and efficacy of sofosbuvir may be reduced by intestinal P-glycoprotein inducers. CBZ may or may not be an inducer of intestinal P-glycoprotein; this effect is unclear. ADVICE: Do not use.

DACLATASVIR:

- **Risperidone:** Moderate interaction. Daclatasvir may increase levels of risperidone via P-glycoprotein/ABCB1 inhibition. ADVICE: Monitor for risperidone toxicity and adjust dose accordingly.
- **Carbamazepine (CBZ):** Major interaction. CBZ may reduce the levels and efficacy of daclatasvir via CYP3A4 induction. ADVICE: Do not use.

LEDIPASVIR:

- **Risperidone:** Moderate interaction. Ledipasvir may increase levels of risperidone via P-glycoprotein/ABCB1 inhibition. ADVICE: Monitor for risperidone toxicity and adjust dose accordingly.
- **Carbamazepine (CBZ):** Major interaction. Levels and efficacy of ledipasvir may be reduced by intestinal P-glycoprotein inducers. CBZ may or may not be an inducer of intestinal P-glycoprotein; this effect is unclear. ADVICE: Do not use.

Glossary

Bipolar disorder:
A person with bipolar disorder experiences episodes in which their mood and activity levels are significantly disturbed. They may experience periods of elevated mood and increased energy and activity (mania), as well as periods of low mood and decreased energy and activity (depression).

Collaborative care:
A model of care in which physical and mental health services are integrated. It is a multi-professional approach to patient care with a structured management plan, scheduled patient follow□up, and enhanced inter□professional communication.

Cognitive behavioural therapy:
Cognitive behavioural therapy (CBT) aims to address negative feelings by understanding thoughts and behaviours that lead to these feelings. A CBT therapist helps a person identify distorted thoughts and maladaptive behaviours.

Contingency management therapy:
Contingency management therapy is a form of therapy that involves encouraging positive, desired behaviours through rewards. Examples of desired behaviours include participating in treatment and reducing harmful substance use. It is recommended as a form of therapy for persons with alcohol or drug use disorders.

Depression, moderate to severe:
A person with moderate to severe depression typically may experience low mood, loss of interest or pleasure in activities, or low energy for at least two weeks or more. Additional symptoms may include reduced concentration and attention, reduced self-esteem and self-confidence, excessive feelings of guilt or unworthiness, bleak or pessimistic views of the future, disturbed sleep, diminished appetite, or ideas or attempts of self-harm or suicide.

Fixed-dose combination:
A fixed-dose combinations (FDC) is a combination of two or more medications in one pill, the goal of which is to simplify medication regimens. FDCs have been shown to increase adherence, decrease prescribing mistakes, and streamline procurement.

Glycaemic control:
Refers to control of blood sugar levels in patients with diabetes mellitus.

GRADE methodology:
Grading of Recommendations Assessment, Development, and Evaluation (GRADE) methodology is an internationally agreed upon standard for rating the quality of studies included in a systematic review according to study design, risk of bias, inconsistency, indirectness, imprecision, and publication bias.

Iatrogenic effects:
Refer to the unintended side effects or health consequences of prescribed medication or other healthcare interventions.

Motivational interviewing or motivational enhancement therapy:
Motivational interviewing or motivational enhancement therapy is a type of therapy that engages a person in a discussion about their behaviour and what they perceive as the benefits and harms of this behaviour, with the goal of supporting behaviour change.

Noncommunicable diseases:
Noncommunicable diseases (NCDs) encompass all diseases that are not infectious in origin. The term NCDs commonly refers to mental disorders, cardiovascular diseases, diabetes, respiratory illnesses, and cancers.

Obese:
Excess weight, defined by a body-mass-index (BMI) of greater than or equal to 25 and less than 30.

Overweight:
Excess weight, defined by a body-mass-index (BMI) of greater than or equal to 30.

Severe mental disorders:
A group of conditions that include moderate to severe depression, bipolar disorder, and schizophrenia and other psychotic disorders

Schizophrenia:
Schizophrenia is a chronic psychotic disorder, which is characterized by distortions of thinking and/or perception. Schizophrenia may manifest by disorganized thinking, paranoia or suspiciousness, delusional beliefs, altered perceptions or hallucinations, limited range of emotions, and/or impaired functioning.

Social determinants of health:
Defined as the social circumstances across a lifetime in which people are born, raised, and live their lives. Inequitable distribution of resources impact these conditions and subsequently impact numerous health outcomes.

Universal health coverage:
Universal health coverage (UHC) is a principle by which all persons have access to essential health care without onerous out-of-pocket expenditures.

For further information, please contact:

Department of Mental Health and
Substance Abuse,
World Health Organization
Avenue Appia 20, CH-1211 Geneva 27
Switzerland

Email: mhgap-info@who.int
Website: www.who.int/mental_health

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