

## Supplemental Online Content

Orkin AM, Gill PJ, Ghersi D, et al; CONSERVE Group. Guidelines for reporting trial protocols and completed trials modified due to the COVID-19 pandemic and other extenuating circumstances: the CONSERVE 2021 statement. *JAMA*. Published online June 21, 2021. doi:10.1001/jama.2021.9941

**eAppendix 1.** Summary of Survey of Trial Professionals

**eAppendix 2.** Summary Rapid Review Findings

**eAppendix 3.** Search Strategies

This supplemental material has been provided by the authors to give readers additional information about their work.

# eAppendix 1. Summary of Survey of Trial Professionals

## Survey Summary

The final stage of the CONSERVE development process was a survey of global professionals involved in trial implementation and publication. The survey described the aims of CONSERVE, shared an earlier version of the CONSERVE implementation tool as well as definitions of terms and concepts that had already achieved consensus among the CONSERVE panel members, and provided a list of panel members.

This survey was designed to solicit professional feedback and expertise from the global trials community to refine the reporting guideline and identify case studies for inclusion in the CONSERVE report. The survey was intended for anyone involved in their professional capacity in the conduct of trials related to health. This includes investigators, sponsors, funders, regulators, editors and publishers. The survey was designed to take less than 15 minutes and user tested among members of the CONSERVE panel.

The survey was distributed by many CONSERVE Panelists within their professional networks (panelists whose professional affiliations did not permit this kind of distribution refrained from doing so). Our goal was to receive more than 100 responses with representation from a variety of professional backgrounds as well as representatives from all continents (except Antarctica).

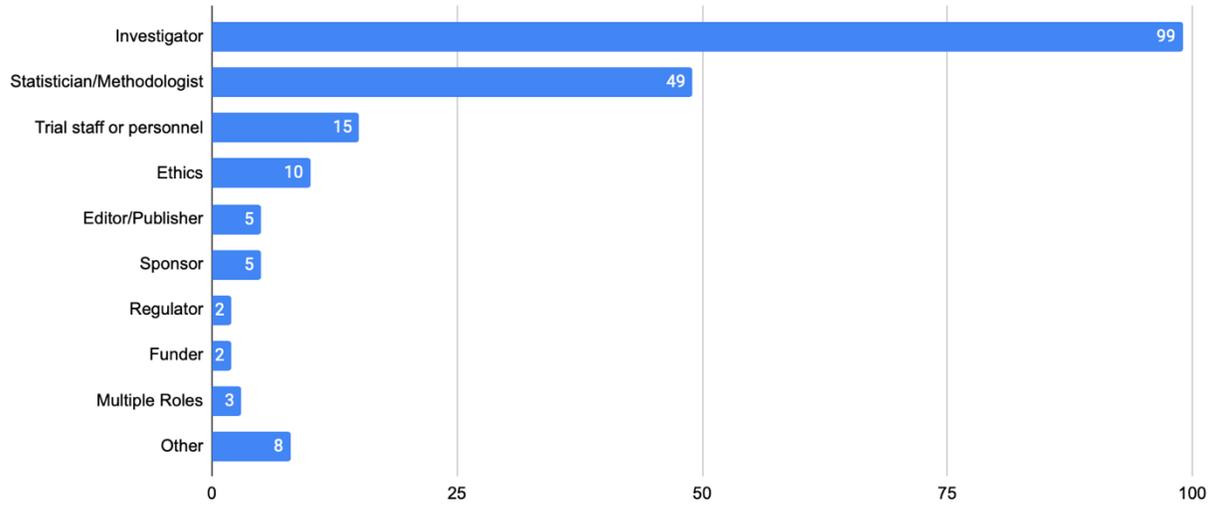
This survey did not constitute human subjects research as defined by the Tri-Council Policy Statement (Canada) and as such it fell outside the scope of Research Ethics Board review. Therefore, the findings were also not analysed as a research exercise.

The table and graphs below summarize the survey questions and findings.

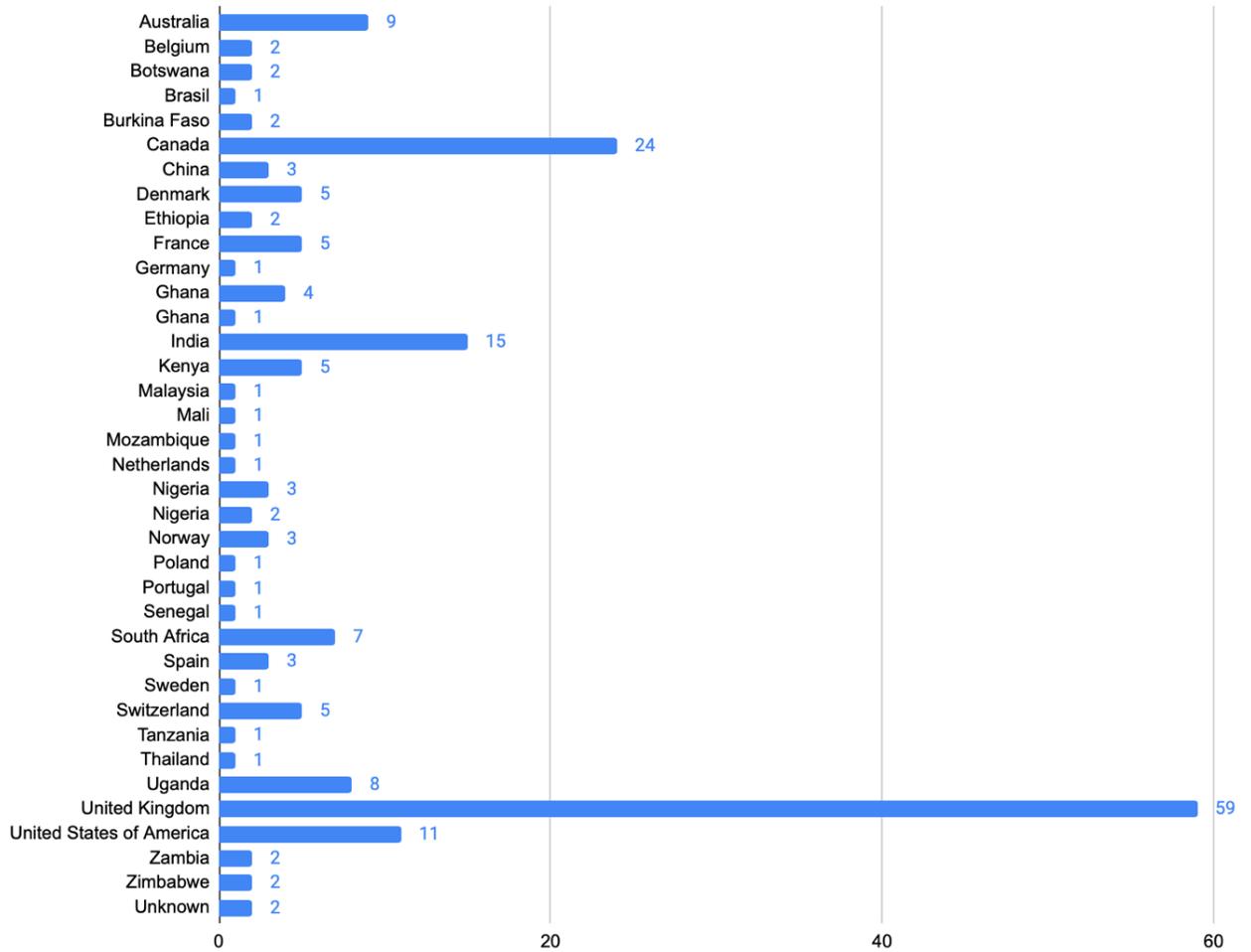
<b>Table Supp1: Survey of Trial Professionals, Questions and Findings</b>	
<b>Question</b>	<b>Summary Response/ Comments N=198</b>
<p><b>A: [Draft Definitions of key concepts provided]</b></p> <ul style="list-style-type: none"> <li>- <b>Please select the option below that best describes your opinion regarding these definitions:</b> <ul style="list-style-type: none"> <li>a. <b>These definitions make sense to me. I understand and can use the concepts.</b></li> <li>b. <b>One or more of these definitions is not clear and requires revisions.</b></li> </ul> </li> </ul> <p><b>If b: In your opinion, what revisions would improve the clarity of these concepts? Please indicate which item needs revision and describe the revisions needed to make the concept more useful to you.</b></p>	<p>178 (90%) of participants indicated that they understood the concept definitions.</p>
<p><b>B: [Draft CONSERVE algorithm provided (subsequently renamed "Implementation Tool")]</b></p> <ul style="list-style-type: none"> <li>- <b>Please select the option that best describes your opinion regarding the algorithm above.</b> <ul style="list-style-type: none"> <li>a. <b>This algorithm makes sense to me. I understand it and could use it.</b></li> <li>b. <b>This algorithm is not clear and requires revisions.</b></li> </ul> </li> </ul>	<p>169 (85.4%) of participants indicated that they understood and could use the algorithm.</p>

<b>If b: If you think that revisions are required, what would improve the algorithm? (optional)</b>	
<p><b>C: Your experience with trials facing major [important] modifications in extenuating circumstances.</b></p> <ul style="list-style-type: none"> <li>- <b>Have you ever been engaged with a trial that had to undergo major [important] modifications in extenuating circumstances?</b> <ul style="list-style-type: none"> <li>a. <b>No; b. Yes; If b:</b> <ul style="list-style-type: none"> <li>i) <b>What was your role in the trial that faced major [important] modifications? (investigator, trial coordinator/manager, sponsor, regulator, funder, editor/publisher, ethics, statistician/methodologist, other...)</b></li> <li>ii) <b>Please describe the extenuating circumstance.</b></li> <li>iii) <b>At what stage of the trial did the extenuating circumstance take effect?</b> <ul style="list-style-type: none"> <li>a. <b>Prior to recruitment</b></li> <li>b. <b>When less than half of participants had been recruited</b></li> <li>c. <b>When more than half of participants had been recruited</b></li> <li>d. <b>After trial completion</b></li> </ul> </li> <li>iv) <b>Please describe the impacts on the trial.</b></li> <li>v) <b>Please describe the mitigating strategies used to manage the situation.</b></li> </ul> </li> </ul> </li> </ul>	Data gathered to help identify case studies.
<p><b>D: Your information</b></p> <ul style="list-style-type: none"> <li>- <b>Name</b></li> <li>- <b>Country where you work</b></li> <li>- <b>Title and affiliation</b></li> <li>- <b>What is your primary professional role in trials? (investigator, sponsor, regulator, funder, editor/publisher, ethics, statistician/methodologist)</b></li> <li>- <b>What is your preferred email address?</b></li> <li>- <b>May we contact you by email for more information about your responses, if necessary?</b></li> <li>- <b>Do you want to receive a small number of email updates about CONSERVE?</b></li> </ul>	See below.
<p><b>E: General comments</b></p> <ul style="list-style-type: none"> <li>- <b>Please provide any general comments about CONSERVE.</b></li> </ul>	All feedback incorporated into revisions.

### Respondent's Primary professional role in trials

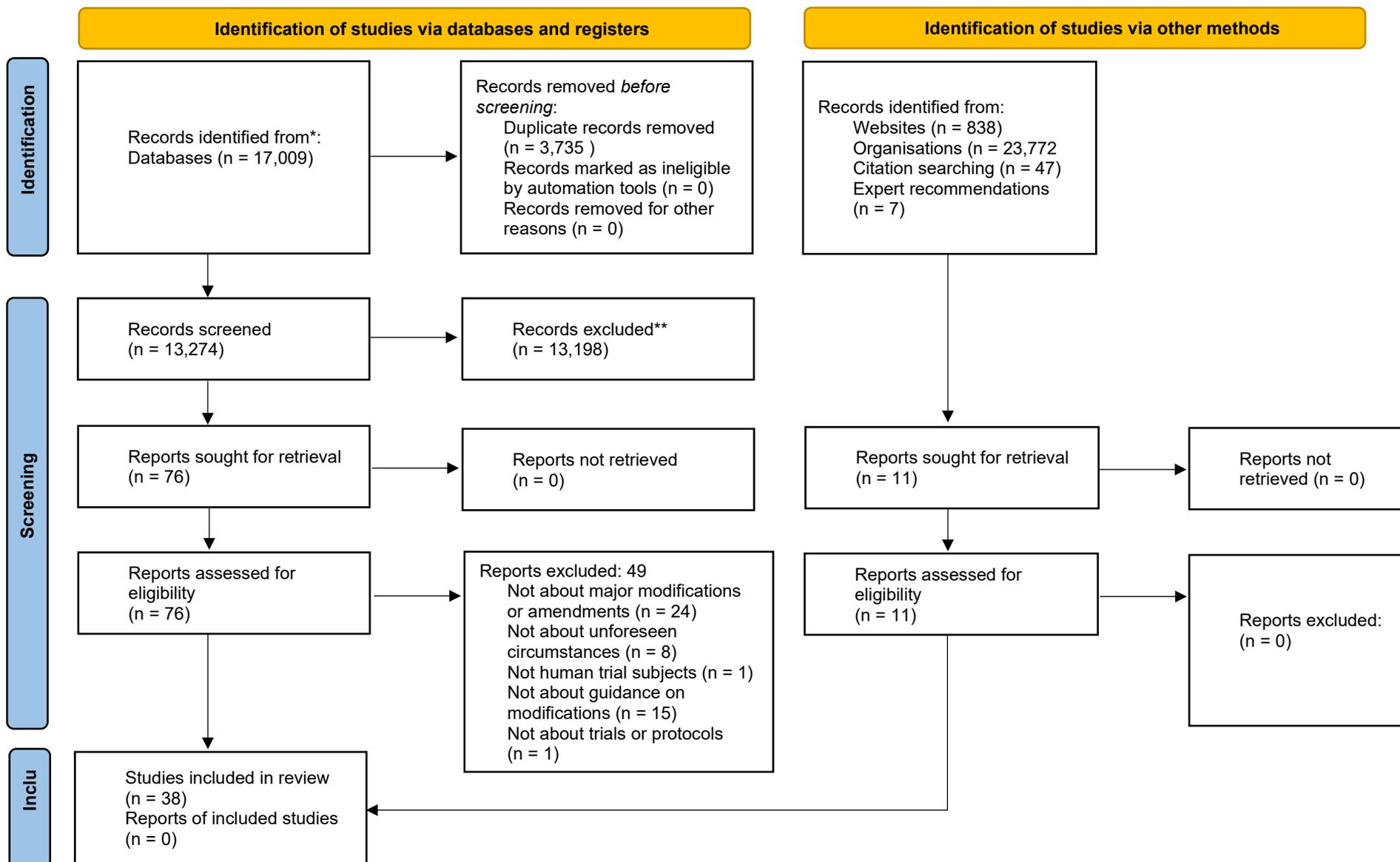


### Country where the majority of the respondent's trial work occurs



## eAppendix 2. Summary Rapid Review Findings

Figure Supp 2. CONSERVE Rapid review PRISMA 2020 flow diagram



\*Consider, if feasible to do so, reporting the number of records identified from each database or register searched (rather than the total number across all databases/registers).

\*\*If automation tools were used, indicate how many records were excluded by a human and how many were excluded by automation tools.

*From:* Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ* 2021;372:n71. doi: 10.1136/bmj.n71. For more information, visit: <http://www.prisma-statement.org/>

**Table Supp 2.** List of regulatory agencies reporting recommendations for important modifications due to extenuating circumstances due to COVID-19 pandemic (n=10).

Name, Year, Country	Title	Reporting recommendations for important modifications
Bulgaria Drug Agency <sup>1</sup> March 2020 Bulgaria	Recommendations to COVID-19 clinical trial sponsors.	None
CTPG, NHMRC, TGA <sup>2</sup> 2020 Australia	COVID-19: Guidance on clinical trials for institutions, HRECs, researchers and sponsors	None
EMA <sup>3</sup> March 2020 Europe	Guidance on the management of clinical trials during the COVID-19 (coronavirus) pandemic	Drafted points to consider on implications of Coronavirus disease (COVID-19) on methodological aspects of ongoing clinical trials (e.g. describing specific dates and durations of issues external to the trial, considerations when data review may be warranted to inform study decisions) Recommend reporting results of adjusted monitoring/review measures and their effects in monitoring reports and clinical study reports
FDA <sup>4,5</sup> April 2020 US	FDA guidance on conduct of clinical trials of medical products during COVID-19 pandemic: guidance for industry, investigators, and institutional review boards  FDA guidance on Statistical Considerations for Clinical Trials During the COVID-19 Public Health Emergency Guidance for Industry	Describe in clinical study report or separate document: 1) contingency measures implemented; 2) listing of all participants affected including how participation was altered; and 3) analyses and discussions that address the effect of implemented changes on safety and efficacy of results
Health Canada <sup>6</sup> Sept 2020 Canada	Management of clinical trials during the COVID-19 pandemic: Notice to clinical trial sponsors	None
Instituto Nacional de Vigilancia de	Lineamientos investigación clínica coronavirus (COVID-19)	None

**Table Supp 2.** List of regulatory agencies reporting recommendations for important modifications due to extenuating circumstances due to COVID-19 pandemic (n=10).

Name, Year, Country	Title	Reporting recommendations for important modifications
Medicamentos y Alimentos <sup>7</sup> March 2020 Columbia		
MHRA <sup>8</sup> March 2020 UK	Managing clinical trials during coronavirus (COVID-19): how investigators and sponsors should manage clinical trials during COVID-19.	None
NoMA <sup>9</sup> March 2020 Norway	Management of clinical trials in relation to COVID-19	Recommend adding an appendix to study protocol outlining all substantial and non-substantial changes due to COVID-19 pandemic
SAHPRA <sup>10</sup> March 2020 South Africa	SAHPRA Policy on Conduct of Clinical Trials of Health Products During the Current COVID-19 Pandemic	Describe modifications in clinical study reports Consistent recommendations to FDA
State Institute for Drug Control <sup>11</sup> March 2020 Czech Republic	Opinion of SÚKL's department of clinical trials on medicinal products on ongoing clinical trials and to-be commenced clinical trials in light of the COVID-19 epidemiological situation.	None

CTPG, Clinical Trials Promoting Group; EMA, European Medicines Agency; FDA, Food and Drug Administration; MHRA, Medicines and Healthcare products Regulatory Agency; NHMRC, National Health and Medical Research Council; NoMa, Norwegian Medical Agency; SAHPRA, South African Health Products Regulatory Authority; TGA, Therapeutic Goods Administration;

**Table Supp 3.** List of articles identified and key points related to reporting recommendations for important modifications due to extenuating circumstances (n=28)

Author*, Year, Journal	Title	Article type, Country**	Key points
Alirol <sup>12</sup> 2017 <i>BMC Medical Ethics</i>	Ethics review of studies during public health emergencies - the experience of the WHO ethics review committee during the Ebola virus disease epidemic.	Article, Switzerland	Outlines key principles for ethics committee review and approval for studies conducted during public health emergencies, such as issues with patients lost to follow-up, patients affected by emergency, and changes to treatment/standard of care
AlNaami <sup>13</sup> 2020 <i>World J Clin Cases</i>	Medical research during the COVID-19 pandemic	Commentary, Canada	Outlines importance of developing a process to identify, document, and report protocol deviations to assist in interpretation of study findings
Anker <sup>14</sup> 2020 <i>European Heart Journal</i>	Conducting clinical trials in heart failure during (and after) the COVID-19 pandemic: An Expert Consensus Position Paper from the Heart Failure Association (HFA) of the European Society of Cardiology (ESC)	Position paper, Germany	Sponsors should describe in clinical study report any changes or measures due to COVID-19 pandemic Trial registration sites should create section to report changes or modifications due to COVID-19 pandemic
Beane <sup>15</sup> 2020 <i>Annals of Surgery</i>	Conducting Clinical Trials in the Time of a Pandemic.	Commentary, US	Outlines processes and principles for trial modification during COVID-19 pandemic with prioritization of patient safety, illustrated with hypothetical examples.
Coleman <sup>16</sup> 2020 <i>Transl Behav Med</i>	Adapting to disruption of research during the COVID-19 pandemic while testing nonpharmacological approaches to pain management	Article, US	Describes steps taken by NIH Department of Defense Department of Veterans Affairs Pain Management Collaboratory to address response to COVID-19 pandemic of 11 large pragmatic trials. Outlined processes taken by each trial by developing: i) harmonized participant questionnaires to assess effect of

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Author*, Year, Journal	Title	Article type, Country**	Key points
			the COVID-19 pandemic on health outcomes; and ii) harmonized surveys of collaborators to capture changes and monitor the effect on research practices (e.g. intervention, data collection, trial integrity, recruitment, and statistical analyses). These steps were taken to help support later data synthesis
Cro <sup>17</sup> 2020 <i>BMC Medical Research</i>	A four-step strategy for handling missing outcome data in randomised trials affected by a pandemic	Methods Articles, UK	Outline four-step strategy for handling missing outcome data, including: 1) clarify treatment estimate obtained from trial; 2) establish what data are missing; 3) conduct primary analysis under most plausible missing data assumptions; and 4) perform sensitivity analyses Trialists should be transparent and report all criteria used to inform the analysis
Dahne <sup>18</sup> 2020 <i>Nicotine &amp; Tobacco Research</i>	Remote Methods for Conducting Tobacco-Focused Clinical Trials	Review, US	Outline methods to conduct tobacco-focused trials remotely
Davis <sup>19</sup> 2020 <i>Perspectives in Clinical Research</i>	Challenges and opportunities for sponsors in conducting clinical trials during a pandemic	Commentary, India	Describes challenges for sponsors in dealing with trials during and post COVID-19 pandemic, with unique considerations for studies conducted in India
de Paula <sup>20</sup> 2020 <i>The Lancet Oncology</i>	Recommendations from national regulatory agencies for ongoing cancer trials during the COVID-19 pandemic	Letter, UK	Summarizes the effect of the COVID-19 pandemic on oncology trials, including summarizing guidance from key regulatory agencies for clinical trials during the pandemic

**Table Supp 3.** List of articles identified and key points related to reporting recommendations for important modifications due to extenuating circumstances (n=28)

Author*, Year, Journal	Title	Article type, Country**	Key points
Dipasquale <sup>21</sup> 2020 <i>Frontiers in Oncology</i>	Conducting Phase I Trials During the SARS-Coronavirus-2 Outbreak: About Science and Care	Commentary, Italy	Describe experience of Phase 1 clinical trials in Oncology and modifications made to recruit and conduct the trials, mainly for safety and for site-specific issues
Fleming <sup>22</sup> 2020 <i>JAMA</i>	Conducting Clinical Research during the COVID-19 Pandemic: Protecting Scientific Integrity	Commentary, US	Discusses the procedures for the COVID-19 pandemic to ensure safety of participants while mitigating risks to trial integrity. Suggests protocol amendments be clearly outlined and dated, transparent which review committee and regulatory boards reviewed, and detailed in methods section of the final research report or protocol amendment and highlighted in the cover letter.
Frey <sup>23</sup> 2021 <i>Molecular Genetics and Metabolism</i>	Measures to mitigate disruption due to the COVID-19 pandemic of the MODIFY phase 3 pivotal trial in patients with Fabry disease	Commentary, Switzerland	Discusses temporary measures (through a protocol addendum) to preserve patient safety, trial integrity and interpretability, in compliance with regulatory requirements to mitigate the effect of the pandemic on MODIFY. Suggests investigators conduct remote visits to decrease risk to patients and minimize missing data, and had the study treatment shipped to patients' homes.
Gobat <sup>24</sup> 2018 <i>The Lancet</i>	Preparedness for clinical research during pandemics: a perspective from the Platform for European Preparedness Against (Re-) emerging Epidemics (PREPARE)	Article, Wales/Europe	Outlines how a pre-funded clinical research network could be utilized during a pandemic to rapidly scale up trials, using influenza as a hypothetical example
Gongoria <sup>25</sup> 2020 <i>Oncology (Williston Park)</i>	Oncology Clinical Trials During the COVID-19 Pandemic	Commentary, Brazil	Discusses challenges to oncology trials due to COVID-19 pandemic. Recommends that clinical study reports include all contingency measures and protocol deviations in trial.

**Table Supp 3.** List of articles identified and key points related to reporting recommendations for important modifications due to extenuating circumstances (n=28)

Author*, Year, Journal	Title	Article type, Country**	Key points
Guo <sup>26</sup> 2020 <i>Statistics in Biopharmaceutical Research</i>	Operational Experiences in China and Statistical Issues on the Conduct of Clinical Trials During the COVID-19 Pandemic	Article, Taiwan	The article refers to the FDA and EMA guidelines. The article describes challenges in patient recruitment may arise from quarantines, site closures, travel limitations, or other considerations if site personnel or trial subjects become infected with COVID-19. Discusses the use of remote data monitoring to safely, and effectively, reach patients and to continue to collect as much data as possible.
Lau APASL COVID-19 Task Force <sup>27</sup> 2020 <i>Hepatology International</i>	Clinical practice guidance for hepatology and liver transplant providers during the COVID-19 pandemic: APASL expert panel consensus recommendations	Practice Guideline, China	Suggest trialists describe and submit list of protocol deviations due to COVID-19 pandemic to IRB
Malalasekera <sup>28</sup> 2020 <i>Asia-Pacific Journal of Clinical Oncology</i>	ZENERGISE trial and COVID-19 tribulation: A snapshot of progress	Australia	Describe major modifications implemented to single-group feasibility trial in response to the COVID-19 pandemic, including detailed timeline of changes
Marcum <sup>29</sup> 2020 <i>Cancer Medicine</i>	COVID-19 pandemic and impact on cancer clinical trials: An academic medical center perspective	Commentary, US	Local IRBs released guidance on reporting of COVID-19 related protocol deviations.
McDermott <sup>30</sup> 2020 <i>JAMA</i>	Preserving Clinical Trial Integrity During the Coronavirus Pandemic.	Commentary, US	Challenges related to COVID-19 pandemic in clinical trials should be described in the methods section

<b>Table Supp 3.</b> List of articles identified and key points related to reporting recommendations for important modifications due to extenuating circumstances (n=28)			
<b>Author*, Year, Journal</b>	<b>Title</b>	<b>Article type, Country**</b>	<b>Key points</b>
Meagher <sup>31</sup> 2020 <i>Mayo Clinic Proceedings</i>	COVID-19 Ethics and Research	Commentary, US	Refers to FDA guidelines on reporting the effects of COVID-19 in study reports
Moskowitz <sup>32</sup> 2020 <i>JAMA Oncology</i>	Implications for Design and Analyses of Oncology Clinical Trials during the COVID-19 Pandemic	Commentary, US	Recommend reporting results separately, divided by time before COVID-19 pandemic, time period when the effect of pandemic is greatest, and data after pandemic (if applicable; either combined with pre-pandemic or separate) Recommend sensitivity/additional planned analyses excluding patients affected due to restrictions during COVID-19 pandemic; document and report reasons for exclusions Additional sensitivity analyses may be needed focused on censoring at time of death
Parikh <sup>33</sup> 2020 <i>Indian Journal of Medical and Paediatric Oncology</i>	Serious Adverse Events' faced by clinical trials: Impact of the COVID-19 pandemic	Commentary, India	Recommend that authors must describe and report changes to protocol or study when presenting at conferences or submitting manuscripts
Perlis <sup>34</sup> 2021 <i>JAMA Network Open</i>	Reporting Clinical Studies Affected by the COVID-19 Pandemic: Guidelines for Authors	Editorial, US	Studies affected by pandemic should create an additional section in methods called "Changes in Response to the COVID-19 Pandemic" to describe changes in study protocol, any trial delays or interruptions, issues with missing data and statistical power
Pothuri <sup>35</sup> 2020 <i>Gynecologic Oncology</i>	Anti-cancer therapy and clinical trial considerations for gynecologic oncology patients during the COVID-19 pandemic crisis	Article, US	Refer to local institutional regulatory guidelines for reporting and describing COVID-19 related modifications

<b>Table Supp 3.</b> List of articles identified and key points related to reporting recommendations for important modifications due to extenuating circumstances (n=28)			
<b>Author*, Year, Journal</b>	<b>Title</b>	<b>Article type, Country**</b>	<b>Key points</b>
Rubio-San-Simón <sup>36</sup> 2020 <i>Clinical &amp; Translational Oncology</i>	Challenges in early phase clinical trials for childhood cancer during the COVID-19 pandemic: a report from the new agents group of the Spanish Society of Paediatric Haematology and Oncology (SEHOP)	Article, Spain	Describe the effect of COVID-19 pandemic on early-phase clinical trials in pediatric cancer
Rusen <sup>37</sup> 2020 <i>Tropical Medicine and Infectious Disease</i>	Challenges in Tuberculosis Clinical Trials in the Face of the COVID-19 Pandemic: A Sponsor's Perspective	Commentary, US	Essential to carefully document protocol deviations during pandemic
Vissers <sup>38</sup> 2020 <i>British Journal of Clinical Pharmacology</i>	The impact of the global COVID-19 pandemic on the conduct of clinical trials: Return to normalcy by considering the practical impact of a structured ethical analysis	Commentary, Netherlands	Modifications and re-starting clinical trials during pandemic must consider ethical issues
Waterhouse <sup>39</sup> 2020 <i>JCO Oncology Practice</i>	Early Impact of COVID-19 on the Conduct of Oncology Clinical Trials and Long-Term Opportunities for Transformation: Findings from an American Society of Clinical Oncology Survey	Commentary, survey US	Reinforces importance of detailed documentation and reporting of procedures, modifications or protocol deviations

\*Last name of first author.

\*\*Country of origin of corresponding author.

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### *eAppendix 3. Search Strategies*

All database searches were updated February 26, 2021

Database(s): **Ovid MEDLINE: Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE® Daily and Ovid MEDLINE® 1946-Present**

Search Strategy:

#	Searches	Results
1	Emergencies/	41148
2	exp Coronavirus/	60501
3	exp Coronavirus Infections/	71770
4	(coronavirus* or corona virus* or OC43 or NL63 or 229E or HKU1 or HCoV* or ncov* or covid* or sars-cov* or sarscov* or Sars-coronavirus* or Severe Acute Respiratory Syndrome Coronavirus*).mp.	126541
5	(or/2-4) and ((20191* or 202*).dp. or 20190101:20301231.(ep).) [this set is the sensitive/broad part of the search]	113552
6	5 or (ebola or SARS or SARS-CoV or MERS or MERS-CoV or Middle East respiratory syndrome or camel* or dromedar* or equine or coronary or coronal or covidence* or covidien or influenza virus or HIV or bovine or calves or TGEV or feline or porcine or BCoV or PED or PEDV or PDCoV or FIPV or FCoV or SADS-CoV or canine or CCov or zoonotic or avian influenza or H1N1 or H5N1 or H5N6 or IBV or murine corona*).mp. [line 5 removes noise in the search results]	1575479
7	((pneumonia or covid* or coronavirus* or corona virus* or ncov* or 2019-ncov or sars*).mp. or exp pneumonia/) and Wuhan.mp.	4624
8	(2019-ncov or ncov19 or ncov-19 or 2019-novel CoV or sars-cov2 or sars-cov-2 or sarscov2 or sarscov-2 or Sars-coronavirus2 or Sars-coronavirus-2 or SARS-like coronavirus* or coronavirus-19 or covid19 or covid-19 or covid 2019 or ((novel or new or nouveau) adj2 (CoV on nCoV or covid or coronavirus* or corona virus or Pandemi*2)) or ((covid or covid19 or covid-19) and pandemic*2) or (coronavirus* and pneumonia)).mp.	111994
9	COVID-19.rx,px,ox. or severe acute respiratory syndrome coronavirus 2.os.	3188

10	("32240632" or "32236488" or "32268021" or "32267941" or "32169616" or "32267649" or "32267499" or "32267344" or "32248853" or "32246156" or "32243118" or "32240583" or "32237674" or "32234725" or "32173381" or "32227595" or "32185863" or "32221979" or "32213260" or "32205350" or "32202721" or "32197097" or "32196032" or "32188729" or "32176889" or "32088947" or "32277065" or "32273472" or "32273444" or "32145185" or "31917786" or "32267384" or "32265186" or "32253187" or "32265567" or "32231286" or "32105468" or "32179788" or "32152361" or "32152148" or "32140676" or "32053580" or "32029604" or "32127714" or "32047315" or "32020111" or "32267950" or "32249952" or "32172715").ui. [Articles not captured by this search when created in April 2020, pending further indexing by NLM]	49
11	or/7-10 [Lines 6 to 9 are specific to Covid-19]	112060
12	6 or 11	1575969
13	12 and 20191201:20301231.(dt). [OVID Medline expert June 2]	183273
14	((wuhan or beijing or shanghai or korea or spain or portugal or italy or usa or uk or brazil or france or mexico) adj2 corona*).mp.	247
15	((wuhan or beijing or shanghai or korea or spain or portugal or italy or USA or UK or brazil or france or mexico) adj2 pneumoni*).mp.	393
16	(wuhan or beijing or shanghai or korea or italy or spain or usa or uk or brazil or france or mexico).mp. and (exp coronavirus/ or exp pneumonia/)	13362
17	(exp china/ or exp korea/ or exp Europe/ or north america/ or canada/ or mexico/ or united states/) and (exp coronavirus/ or exp pneumonia/)	26193
18	("corona viru*" or "nCov" or "2019 ncov" or "Novel Coronavirus" or "covid-19" or "SARS-COV-2" or "Severe Acute Respiratory Syndrome Coronavirus 2" or "coronavirus disease 2019" or "corona virus disease 2019").tw,kf.	107123
19	("new coronaviru*" or "2019 ncov" or "nCov 2019" or "SARS Coronavirus 2" or "novel coronaviru*").mp.	9725
20	"Severe Acute Respiratory Syndrome Coronavirus 2".mp.	11206
21	((new or novel or emerging or "2020") adj2 (coronaviru* or "corona viru*")).tw,kf.	308
22	((pandemic or epidemic or "global spread") adj3 (coronavir* or corona or covid or "2020")).mp.	37259
23	("2020" adj2 (pandemic or epidemic or "global disease spread" or "virus spread")).mp.	435
24	("Novel Corona virus" or "corona virus disease 2019" or "nCov 2019" or "SARS Coronavirus 2" or "COVID-2019" or nCoV or "2019-nCoV" or covid19 or " covid-19" or "SARS-CoV-2").tw,kf.	104646

25	coronavir*.mp.	82942
26	or/13-25 [COVID textwords + Mesh]	20692
27	exp Accidents/	195001
28	civil disorders/ or riots/ or exp terrorism/ or exp "warfare and armed conflicts"/	53647
29	disasters/ or mass casualty incidents/ or exp natural disasters/	36660
30	Hemorrhagic Fever, Ebola/ or disease outbreaks/ or epidemics/ or pandemics/	145570
31	middle east respiratory syndrome coronavirus/ or sars virus/	5018
32	(war or warfare or armed conflict* or disaster* or accident* or emergenc* or civil* unrest or civil violen* or terrorism* or bioterrorism* or pandemic* or epidemic*).tw,kf.	744360
33	((chemical or nuclear or natural) adj2 (hazard* or accident* or disaster*)).tw,kf.	9633
34	((disease* or virus or viral) adj2 (outbreak* or global spread)).tw,kf.	11943
35	(mass adj2 (shooting or casual*)).tw,kf.	2682
36	exp clinical trial/ or clinical trial protocol/	888105
37	exp Clinical Trials as Topic/	353300
38	((major* or substantial* or extraordinary or meaningful or considerable or massive* or significant* or sizeable or consequential* or far-reaching or extensive or extensively) adj3 (amend* or modification* or modify or modified or revision* or revise* or adjust* or alter* or redesign* or change*)).tw,kf.	394373
39	((amend* or modification* or modify or modified or revision* or revise* or adjust* or alter* or redesign*) adj3 (trial* or RCT* or protocol* or research stud* or clinical stud*)).tw,kf.	15515
40	((unplanned or unforese* or unanticipate* or unexpecte#d* or extenuating or startling or abrupt or unprecedented* or "not planned" or unavoidable or cris?s or emergency or emergencies) adj3 (circumstance* or situation* or event*)).tw,kf.	9917
41	((major* or substantial* or extraordinary or meaningful or considerable or massive* or significant* or sizeable or consequential or far-reaching or extensive or extensively) adj3 chang* adj3 (protocol* or trial* or rct* or "research stud*" or "clinical stud*")).tw,kf.	460
42	clinical trial*.mp. or clinical trial.pt. or random:.mp. or tu.xs.	6070127
43	or/36-37,42 [Clinical Trials]	6070428
44	((unplanned or unforeseen or unanticipated or unexpected##* or sudden* or abrupt* or "not planned" or unavoidable) adj3 (amend* or change* or alter* or modification* or modify or modified or revision* or revise* or redesign* or change*)).tw,kf.	9265

45	or/1-35,40 [Extenuating circumstanes individual MeSH and textwords]	2453941
46	43 and 38 [Trials and major modifications]	124235
47	39 or 41 or 46 [Major modification in trials combined]	139629
48	45 and 47 [Trials and major modifications and extenuating circumstanes]	13457
49	43 and 44 and 45 [Clinical trials and unplanned near modifications and extenuating circumstanes]	173
50	48 or 49 [Trials and major amendments and extenuating circumstanes combined]	13617
51	<b>limit 50 to (humans and yr="2003 -Current")</b>	<b>6779</b>

Database(s): **Embase Classic+Embase** 1947 to 2021 February 26

#	Searches	Results
1	exp coronavirinae/	23383
2	(coronavirus* or corona virus* or OC43 or NL63 or 229E or HKU1 or HCoV* or ncov* or covid* or sars-cov* or sarscov* or Sars-coronavirus* or Severe Acute Respiratory Syndrome Coronavirus*).mp.	139320
3	(SARS or SARS-CoV or MERS or MERS-CoV or Middle East respiratory syndrome or camel* or dromedar* or equine or coronary or coronal or covidence* or covidien or influenza virus or HIV or bovine or calves or TGEV or feline or porcine or BCoV or PED or PEDV or PDCoV or FIPV or FCoV or SADS-CoV or canine or CCov or zoonotic or avian influenza or H1N1 or H5N1 or H5N6 or IBV or murine corona* or ebola).tw,kw.	1720520
4	((pneumonia or covid* or coronavirus* or corona virus* or ncov* or 2019-ncov or sars*).mp. or exp pneumonia/) and Wuhan.mp.	4912
5	(2019-ncov or ncov19 or ncov-19 or 2019-novel CoV or sars-cov2 or sars-cov-2 or sarscov2 or sarscov-2 or Sars-coronavirus2 or Sars-coronavirus-2 or SARS-like coronavirus* or coronavirus-19 or covid19 or covid-19 or covid 2019 or ((novel or new or nouveau) adj2 (CoV on nCoV or covid or coronavirus* or corona virus or Pandemi*2)) or ((covid or covid19 or covid-19) and pandemic*2) or (coronavirus* and pneumonia)).mp.	108581
6	((wuhan or beijing or shanghai or korea or spain or portugal or italy or usa or uk or brazil or france or mexico) adj2 corona*).mp.	318
7	((wuhan or beijing or shanghai or korea or spain or portugal or italy or USA or UK or brazil or france or mexico) adj2 pneumoni*).mp.	503

8	(wuhan or beijing or shanghai or korea or italy or spain or usa or uk or brazil or france or mexico).mp. and (exp coronavirinae/ or exp pneumonia/)	19404
9	(exp china/ or exp korea/ or exp Europe/ or north america/ or canada/ or mexico/ or united states/) and (exp coronavirinae/ or exp pneumonia/)	34681
10	("corona viru*" or "nCov" or "2019 ncov" or "Novel Coronavirus" or "covid-19" or "SARS-COV-2" or "Severe Acute Respiratory Syndrome Coronavirus 2" or "coronavirus disease 2019" or "corona virus disease 2019").tw,kw.	105020
11	("new coronaviru*" or "2019 ncov" or "nCov 2019" or "SARS Coronavirus 2" or "novel coronaviru*").mp.	10538
12	"Severe Acute Respiratory Syndrome Coronavirus 2".mp.	29355
13	((new or novel or emerging or "2020") adj2 (coronaviru* or "corona viru*")).tw,kw.	363
14	((pandemic or epidemic or "global spread") adj3 (coronavir* or corona or covid or "2020")).mp.	35412
15	("2020" adj2 (pandemic or epidemic or "global disease spread" or "virus spread")).mp.	424
16	("Novel Corona virus" or "corona virus disease 2019" or "nCov 2019" or "SARS Coronavirus 2" or "COVID-2019" or nCoV or "2019-nCoV" or covid19 or " covid-19" or "SARS-CoV-2").tw,kw.	102432
17	coronavir*.mp.	126767
18	exp pandemic/ or pandemic influenza/	63156
19	epidemic/ or Ebola hemorrhagic fever/	132632
20	"influenza a virus (h1n1)"/	4488
21	exp Coronavirus infection/	24487
22	exp accident/	227795
23	civil disorder/ or exp violence/	158019
24	exp terrorism/	9658
25	exp war/	39171
26	disaster/ or mass disaster/ or natural disaster/	30687
27	(war or warfare or armed conflict* or disaster* or accident* or emergenc* or civil* unrest or civil violen* or terrorism* or bioterrorism* or pandemic* or epidemic*).tw,kw.	999316
28	((chemical or nuclear or natural) adj2 (hazard* or accident* or disaster*)).tw,kw.	11779
29	((disease* or virus or viral) adj2 (outbreak* or global spread)).tw,kw.	13035
30	(mass adj2 (shooting or casual*)).tw,kw.	3310

31	((unplanned or unforese* or unanticipate* or unexpecte#d* or extenuating or startling or abrupt or unprecedented* or "not planned" or unavoidable or cris?s or emergency or emergencies) adj3 (circumstance* or situation* or event*)).tw,kw.	14624
32	or/1-31 [Extenuating circumstances]	3015904
33	exp clinical trial/	1603044
34	clinical trial*.mp. or clinical trial.pt. or random:.mp.	3007835
35	clinical trial protocol/	907
36	or/33-35 [Clinical trials]	3107790
37	((major* or substantial* or extraordinary or meaningful or considerable or massive* or significant* or sizeable or consequential* or far-reaching or extensive or extensively) adj3 (amend* or modification* or modify or modified or revision* or revise* or adjust* or alter* or redesign* or change*)).tw,kw.	546337
38	((amend* or modification* or modify or modified or revision* or revise* or adjust* or alter* or redesign*) adj3 (trial* or RCT* or protocol* or research stud* or clinical stud*)).tw,kw.	23768
39	((major* or substantial* or extraordinary or meaningful or considerable or massive* or significant* or sizeable or consequential or far-reaching or extensive or extensively) adj3 chang* adj3 (protocol* or trial* or rct* or "research stud*" or "clinical stud*")).tw,kw.	662
40	((unplanned or unforeseen or unanticipated or unexpected#* or sudden* or abrupt* or "not planned" or unavoidable) adj3 (amend* or change* or alter* or modification* or modify or modified or revision* or revise* or redesign* or change*)).tw,kw.	11536
41	38 or 39 [Major amendments to Clinical trials]	24412
42	36 and 37 [Clinical trials AND major amendments]	85672
43	41 or 42 [Major amendments and clinical trials combined]	109387
44	32 and 43 [Major amendments to clinical trials and extenuating circumstances]	10449
45	32 and 36 and 40 [Clinical trials major near amendments and extenuating circumstances]	87
46	44 or 45	10528
47	<b>limit 46 to (human and yr="2003 -Current")</b>	<b>6958</b>

**EBSCO CINAHL Plus Full text**

**TOTAL Results = 3272**

#	Query
S48	S45 OR S47
S47	S43 AND S46
S46	S38 OR S40
S45	S37 AND S44
S44	S42 AND S43
S43	S35 OR S39
S42	S36 OR S41
S41	TI ( (trial* or RCT*) ) OR AB ( (trial* or RCT*) ) TI ( ((major* or substantial* or extraordinary or meaningful or considerable or massive* or significant* or sizeable or consequential or far-reaching or extensive or extensively) N3 chang* N3 (protocol* or trial* or rct* or "research stud*" or "clinical stud*")) ) OR AB ( ((major* or substantial* or extraordinary or meaningful or considerable or massive* or significant* or sizeable or consequential or far-reaching or extensive or extensively) N3 chang* N3 (protocol* or trial* or rct* or "research stud*" or "clinical stud*")) )
S40	TI ( ((unplanned or unforese* or unanticipate* or unexpecte#d* or extenuating or startling or abrupt or unprecedented* or "not planned" or unavoidable or cris?s or emergency or emergencies) N3 (circumstance* or situation* or event*)) ) OR AB ( ((unplanned or unforese* or unanticipate* or unexpecte#d* or extenuating or startling or abrupt or unprecedented* or "not planned" or unavoidable or cris?s or emergency or emergencies) N3 (circumstance* or situation* or event*)) )
S39	TI ( ((amend* or modification* or modify or modified or revision* or revise* or adjust* or alter* or redesign*) N3 (trial* or RCT* or protocol* or research stud* or clinical stud*)) ) OR AB ( ((amend* or modification* or modify or modified or revision* or revise* or adjust* or alter* or redesign*) N3 (trial* or RCT* or protocol* or research stud* or clinical stud*)) )
S38	TI ( ((major* or substantial* or extraordinary or meaningful or considerable or massive* or significant* or sizeable or consequential* or far-reaching or extensive or extensively) N3 (amend* or modification* or modify or modified or revision* or revise* or adjust* or alter* or redesign* or change*). ) OR AB ( ((major* or substantial* or extraordinary or meaningful or considerable or massive* or significant* or sizeable or consequential* or far-reaching or
S37	

extensive or extensively) N3 (amend\* or modification\* or modify or modified or revision\* or revise\* or adjust\* or alter\* or redesign\* or change\*). )

S36 (MH "Clinical Trials+")

S1 OR S12 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S19 OR S20 OR S21 OR S10 OR S11 OR S13 OR S14 OR S22 OR S23 OR S24 OR S25 OR S26 OR S27 OR S28 OR S29 OR S30 OR S31 OR S32 OR S33 OR S34

S35

S34 TI ( (mass N2 (shooting or casual\*)) ) OR AB ( (mass N2 (shooting or casual\*)) )

S33 TI ( ((disease\* or virus or viral) N2 (outbreak\* or global spread)) ) OR AB ( ((disease\* or virus or viral) N2 (outbreak\* or global spread)) )

S32 TI ( ((chemical or nuclear or natural) N2 (hazard\* or accident\* or disaster\*)) ) OR AB ( ((chemical or nuclear or natural) N2 (hazard\* or accident\* or disaster\*)) )

S31 TI ( war or warfare or armed conflict\* or disaster\* or accident\* or emergenc\* or civil\* unrest or civil violen\* or terrorism\* or bioterrorism\* or pandemic\* or epidemic\*. ) OR AB ( war or warfare or armed conflict\* or disaster\* or accident\* or emergenc\* or civil\* unrest or civil violen\* or terrorism\* or bioterrorism\* or pandemic\* or epidemic\*. )

S30 (MH "Hemorrhagic Fever, Ebola")

S29 (MH "Influenza, Pandemic (H1N1) 2009")

S28 (MH "Disease Outbreaks")

S27 (MH "Mass Casualty Incidents")

S26 (MH "Disasters") OR (MH "Natural Disasters+")

S25 (MH "Civil Disorders+")

S24 (MH "Terrorism+")

S23 (MH "War+")

S22 (MH "Accidents+")

S21 TI ( ((new or novel or emerging or "2020") N2 (coronaviru\* or "corona viru\*")) ) OR AB ( ((new or novel or emerging or "2020") N2 (coronaviru\* or "corona viru\*")) )

S20 TI ( new coronaviru\*" or "2019 ncov" or "nCov 2019" or "SARS Coronavirus 2" or "novel coronaviru\*" ) OR AB ( new coronaviru\*" or "2019 ncov" or "nCov 2019" or "SARS Coronavirus 2" or "novel coronaviru\*" )

S19 S17 AND S18

S18 S21 OR S12 OR S15

S17 S1 OR S16

S16 (MH "Pneumonia+")

S15 (MH "North America") OR (MH "Canada+") OR (MH "Mexico") OR (MH "United States+")

S14 TI coronavir\* OR AB coronavir\*

S13 TI ( ("Novel Corona virus" or "corona virus disease 2019" or "nCov 2019" or "SARS  
 Coronavirus 2" or "COVID-2019" or nCoV or "2019-nCoV" or covid19 or " covid-19" or "SARS-  
 CoV-2" ) ) OR AB ( ("Novel Corona virus" or "corona virus disease 2019" or "nCov 2019" or  
 "SARS Coronavirus 2" or "COVID-2019" or nCoV or "2019-nCoV" or covid19 or " covid-19" or  
 "SARS-CoV-2" ) )

S12 (MH "Europe+")

S11 TI ( ("2020" N2 (pandemic or epidemic or "global disease spread" or "virus spread" ) ) OR  
 AB ( ("2020" N2 (pandemic or epidemic or "global disease spread" or "virus spread" ) ) )

S10 TI ( ((pandemic or epidemic or "global spread" ) N3 (coronavir\* or corona or covid or  
 "2020" ) ) OR AB ( ((pandemic or epidemic or "global spread" ) N3 (coronavir\* or corona or  
 covid or "2020" ) ) )

S9 (MH "China+") OR (MH "South Korea") OR (MH "North Korea")

S8 TI ( ("corona viru\*" or "nCov" or "2019 ncov" or "Novel Coronavirus" or "covid-19" or  
 "SARS-COV-2" or "Severe Acute Respiratory Syndrome Coronavirus 2" or "coronavirus disease  
 2019" or "corona virus disease 2019" ) ) OR AB ( ("corona viru\*" or "nCov" or "2019 ncov" or  
 "Novel Coronavirus" or "covid-19" or "SARS-COV-2" or "Severe Acute Respiratory Syndrome  
 Coronavirus 2" or "coronavirus disease 2019" or "corona virus disease 2019" ) )

S7 TI ( ((wuhan or beijing or shanghai or korea or spain or portugal or italy or USA or UK or  
 brazil or france or mexico) N2 pneumoni\* ) ) OR AB ( ((wuhan or beijing or shanghai or korea or  
 spain or portugal or italy or USA or UK or brazil or france or mexico) N2 pneumoni\* ) )

S6 TI ( ((wuhan or beijing or shanghai or korea or spain or portugal or italy or usa or uk or  
 brazil or france or mexico) N2 corona\* ) ) OR AB ( ((wuhan or beijing or shanghai or korea or  
 spain or portugal or italy or usa or uk or brazil or france or mexico) N2 corona\* ) )

S5 TI ( (2019-ncov or ncov19 or ncov-19 or 2019-novel CoV or sars-cov2 or sars-cov-2 or  
 sarscov2 or sarscov-2 or Sars-coronavirus2 or Sars-coronavirus-2 or SARS-like coronavirus\* or  
 coronavirus-19 or covid19 or covid-19 or covid 2019 or ((novel or new or nouveau) adj2 (CoV  
 on nCoV or covid or coronavirus\* or corona virus or Pandemi\*2)) or ((covid or covid19 or  
 covid-19) and pandemic\*2) or (coronavirus\* and pneumonia) ) ) OR AB ( (2019-ncov or ncov19  
 or ncov-19 or 2019-novel CoV or sars-cov2 or sars-cov-2 or sarscov2 or sarscov-2 or Sars-  
 coronavirus2 or Sars-coronavirus-2 or SARS-like coronavirus\* or coronavirus-19 or covid19 or  
 covid-19 or covid 2019 or ((novel or new or nouveau) adj2 (CoV on nCoV or covid or  
 coronavirus\* or corona virus or Pandemi\*2)) or ((covid or covid19 or covid-19) and  
 pandemic\*2) or (coronavirus\* and pneumonia) ) )

S4 TI ( (pneumonia or covid\* or coronavirus\* or corona virus\* or ncov\* or 2019-ncov or sars\*) AND wuhan ) OR AB ( (pneumonia or covid\* or coronavirus\* or corona virus\* or ncov\* or 2019-ncov or sars\*) AND wuhan )

S3 TI ( SARS or SARS-CoV or MERS or MERS-CoV or Middle East respiratory syndrome or camel\* or dromedar\* or equine or coronary or coronal or covidence\* or covidien or influenza virus or HIV or bovine or calves or TGEV or feline or porcine or BCoV or PED or PEDV or PDCoV or FIPV or FCoV or SADS-CoV or canine or CCoV or zoonotic or avian influenza or H1N1 or H5N1 or H5N6 or IBV or murine corona\*). ) OR AB ( SARS or SARS-CoV or MERS or MERS-CoV or Middle East respiratory syndrome or camel\* or dromedar\* or equine or coronary or coronal or covidence\* or covidien or influenza virus or HIV or bovine or calves or TGEV or feline or porcine or BCoV or PED or PEDV or PDCoV or FIPV or FCoV or SADS-CoV or canine or CCoV or zoonotic or avian influenza or H1N1 or H5N1 or H5N6 or IBV or murine corona\*). )

S2 TI ( coronavirus\* or corona virus\* or OC43 or NL63 or 229E or HKU1 or HCoV\* or ncov\* or covid\* or sars-cov\* or sarscov\* or Sars-coronavirus\* or Severe Acute Respiratory Syndrome Coronavirus\* ) OR AB ( coronavirus\* or corona virus\* or OC43 or NL63 or 229E or HKU1 or HCoV\* or ncov\* or covid\* or sars-cov\* or sarscov\* or Sars-coronavirus\* or Severe Acute Respiratory Syndrome Coronavirus\* )

S1 (MH "Coronavirus Infections") OR (MH "Coronaviridae Infections") OR (MH "COVID-19") OR (MH "Middle East Respiratory Syndrome") OR (MH "Severe Acute Respiratory Syndrome")

Grey Literature Search Strategies: Last searched March 6 – 11, 2021

Website Searching Documentation:

Date	Organization name	URL
March 11, 2021	NIH	<a href="https://www.nih.gov/">https://www.nih.gov/</a>
March 11, 2021	WHO	<a href="https://www.who.int/">https://www.who.int/</a>

## Website Searching

All searches were performed using Advanced Google function.

1. [Advanced Google](#) (use Advanced Google to search the **websites** of the relevant authorities/organizations identified in Step 1)
  - Copy & paste the organization's **URL** into Advanced Google's '**site or domain**' field
  - Search with [various word combinations](#) using the most appropriate search box (eg. "all these words", "any of these words", etc)

Select a particular **file type** (ex. PDF) for Google to search

<b>Date</b>	<b>Organization name &amp; website URL</b>	<b>Search strategy(s)/ words searched including (if applicable) how items were selected.</b>  <b>Selection: All results retrieved in the search were reviewed for relevance by 1 reviewer</b>
March 6 2021	Health Canada <a href="https://www.canada.ca/en/health-canada">https://www.canada.ca/en/health-canada</a>	trial* amendment OR modification  <ul style="list-style-type: none"><li>• Selected by 1 reviewer, reviewed by second reviewer in Covidence</li></ul>

March 6 2021	FDA <a href="https://www.fda.gov/home">https://www.fda.gov/home</a>	trial* amendment OR modification  <ul style="list-style-type: none"> <li>Selected by 1 reviewer, scanned first three pages of results</li> </ul>
March 6 2021	Clinical Trials <a href="https://clinicaltrials.gov/">https://clinicaltrials.gov/</a>	Clinicaltrials.gov   trial amendments
March 7 2021	NIH <a href="https://www.nih.gov/">https://www.nih.gov/</a>	<ol style="list-style-type: none"> <li>“Trial amendment” - Selected by 1 reviewer, scanned first page of results</li> <li>“Trial modification” - Selected by 1 reviewer, scanned first page of results</li> </ol>
March 7, 2021	LitCovid	<ol style="list-style-type: none"> <li>major AND (amend* or modif* or change*) AND (trial* or protocol* or RCT*)</li> <li>(halt* or stop*) AND (trial* or protocol* or RCT*)</li> </ol>

*Preprint servers and journals*

*Documentation:*

Date	Database name & URL	Search strategy(s)/ words searched including.  Selection: All results retrieved in the search were reviewed for relevance by 1 reviewer
March 8 2021	OSF PrePrints: <a href="https://osf.io/preprints/">https://osf.io/preprints/</a>	Search strategies:  (trial* OR RCT*) AND (amend* OR modif* OR halt* OR stop* OR change*)  Limited to Subjects: Life Sciences, Medicine and Health Sciences
March 7 2021	Journal of negative results in Biomedicine  <a href="https://jnrbm.biomedcentral.com/">https://jnrbm.biomedcentral.com/</a>	(trial* OR RCT* OR protocol*) AND (amend* or modif*)
March 7 2021	PLOS Collections	(trial* OR RCT* OR protocol*) AND (amend* or modif*)

Search Engine Searching

Various options include Google, [Advanced Google](#), and [customized Google search engines](#)

Documentation:

Date	Search engine	Search strategy(s) including how items were selected
	<i>Ex. Google.ca</i>	Selection: Items were selected by scanning the first 100 results from each search

March 7, 2021	DuckDuckGo	"clinical trial substantial amendments"
March 7, 2021	DuckDuckGo	clinical trial* AND (substantial or major) AND (amend* or modif*)

*Contact Knowledge Experts*

*Documentation:*

Name of individual or listserv	Date contacted (follow up dates if necessary)
CONSERVE group	February 2021