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A Scoping Review of Registered Clinical Trials of Cellular Therapy for COVID-19 and a Framework for Accelerated Synthesis of Trial Evidence—FAST Evidence

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ABSTRACT

The urgent need for safe and effective treatments for COVID-19 has fueled the launch of many parallel complex studies of cellular therapies with small to modest enrolment projections. By pooling data from multiple studies that are similar, we can increase the ability to achieve sufficient power to determine effectiveness more quickly through meta-analysis. A scoping review of registered clinical trials using cell-based interventions for COVID-19 was conducted to identify candidate studies for meta-analysis that could support an accelerated regulatory review. [ClinicalTrials.gov](https://www.clinicaltrials.gov) and WHO International Clinical Trials Registry Platform were searched April 23, 2020. Trials were included if they utilized cell or cell-derived products to treat or prevent COVID-19. Fifty-four registered cellular therapy trials were identified and included for analysis. Studies of mesenchymal stromal cells (MSCs; 41 studies; 1129 subjects projected to receive cells) and natural killer (NK) cells (5 studies; 135 projected to receive cells) were observed most commonly. A subset of studies are controlled (34 studies, or 63%), including 27 studies of MSCs and 3 of NK cells. While heterogeneity in study design exists, the cumulative projected enrolment of patients from similar studies appears sufficient to allow the detection of meaningful differences in clinically important outcomes such as mortality, admission to intensive care and need for mechanical ventilation by September 2020—sooner than any individual study could determine effectiveness. MSCs are the predominant cell type in registered trials for severe or critical COVID-19 and represent the most promising candidates for future meta-analysis. Sufficient pooled sample size to detect clinically important reductions in multiple outcomes, including mortality, is anticipated by September 2020, but may require accessing supplementary data to align outcome reporting. Regulatory approval, funding and implementation by cell manufacturing partners will be accelerated by our framework for rapid meta-analysis.

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Abbreviations: MSC, mesenchymal stromal cell; NK, natural killer; ARDS, acute respiratory distress syndrome; ICU, intensive care unit.

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COVID-19 represents one of the most significant global health crises in recent times [1]. Effective therapies are lacking, and a significant proportion of patients experience progressive dyspnea, hypoxemia and respiratory failure. The acute respiratory distress syndrome (ARDS) is the greatest contributing factor leading to the death of many patients [2]. Cellular therapies such as mesenchymal stromal cells (MSCs) have immune modulating functions that can inhibit the infiltration of inflammatory cells and/or attenuate the expression of cytokines and chemokines that induce damaging inflammation and fibrosis following infection [3,4]. Cell-based therapies for ARDS, other lung diseases and sepsis have been investigated predominantly in pre-clinical animal models [3,4]. Early phase clinical trials have been conducted [5–7] but no cellular therapy has been approved for the treatment of ARDS, sepsis, or cytokine release syndromes, as far as we know. Early phase studies have demonstrated safety and feasibility of treating patients who have ARDS or sepsis with MSCs but remain underpowered to establish efficacy [8]. Moreover, aspects of ARDS in COVID-19 may be distinct from other causes and effectiveness in patients with ARDS related to SARS-Cov-2 will be needed. Greater emphasis on standardized cell manufacturing methods have allowed the field of cellular therapy to mature to a stage where larger scale clinical trials are occurring, however, heterogeneity in the source of cells used to generate various cell products, various components of cell culture methods, and methods of storage and administration need to be carefully considered when pooling data for meta-analysis.

Given the urgency and magnitude of the health challenge posed by COVID-19, health research funding agencies around the world and the biomedical cell manufacturing industry are rapidly pivoting to address COVID-19 and are dedicating significant efforts and funds towards studies for the treatment of COVID-19. Identifying registered studies of cell-based therapy for COVID-19 will identify a network of investigators, allow for the creation of a compendium of actively recruiting registered studies and will allow for the rapid pooling of data that emerges from similar studies to accelerate the assessment of efficacy and also adverse event rates associated with these therapies. Studies are too small in size to determine efficacy on their own without meta-analysis and obtaining supplemental data from investigators will be essential to align outcome measures that are consistent and objective as many studies plan to report surrogate markers of efficacy such as biomarker responses. A Framework for Accelerated Synthesis of Trial Evidence, or FAST Evidence, will be needed to rapidly identify studies that share sufficient homogeneity, obtain the required supplemental data and facilitate a planned meta-analysis in real-time to provide the required knowledge synthesis that could allow timely approval and delivery of effective cellular therapies to treat COVID-19.

Methods

Data Sources and Searches

The registry of clinical trials at clinicaltrials.gov and the WHO International Clinical Trials Registry Platform using the COVID-19 registry of trials were searched on April 23, 2020. The registers were searched for trials of cellular therapy of COVID-19 using the following search strategy (for www.clinicaltrials.gov): (COVID OR “COVID-19” OR “2019-nCoV” OR “novel coronavirus” OR Coronavirus OR “SARS-COV-2” OR SARS) AND (cell OR stem cell OR MSC OR cell therapy OR exosome OR vesicle OR “conditioned media”); and for the WHO registry of COVID-19 studies (www.who.int/ictpr/en/): Cell OR stem cell OR MSC OR exosome OR vesicle OR conditioned media.

Study Selection

Registered clinical studies were included for analysis if they utilized a cell or cell-derived product for interventional purposes to treat or prevent infection of SARS-CoV-2 and its associated disease COVID-19. Registered studies were not included if they did not administer a cell or cell-derived product for interventional purposes to treat or prevent infection of SARS-CoV-2, and if the study was listed as withdrawn or canceled. Registered studies were reviewed by two individuals independently for assessment of inclusion and exclusion criteria.

Data Extraction and Quality Assessment

For each included record, the following data (if available): were extracted by two individuals independently: Trial ID, registry and date of registration, recruiting status, phase, title, planned start date, anticipated primary completion (data collection complete), anticipated study completion, inclusion and exclusion criteria, disease severity, age range of eligible study participants, anticipated number of subjects to be enrolled in both the intervention and control groups (if any), whether randomization is planned, cell type and source, dosage, manufacturing method, whether any cell-derived products are to be given, route of administration, primary and secondary outcomes, country of origin of primary or lead investigator.

Data Synthesis and Analysis

We described the characteristics of all included trials. In order to estimate the required sample size to determine efficacy for a 2, 5, 7.5, and 10% absolute reduction in mortality, we assumed an alpha error of 5% and used a power calculation of 80% and assumed enrolment of subjects in the intervention group was 1:1 compared to control groups. Statistical modeling was done by comparing proportions of two independent groups using a calculator to determine sample size (<https://www.stat.ubc.ca/~rollin/stats/ssize/b2.html>, Department of Statistics, University of British Columbia, Vancouver, Canada) [9]. Graphs were produced using Microsoft Excel (Microsoft Corporation, Redmond, Washington).

Results

A total of 169 records were identified from Clinicaltrials.gov and 142 records from the WHO International Clinical Trials Registry Platform [10]. After removing duplicates, 288 records were reviewed. There were 13 studies that were withdrawn or canceled, leaving 275 for determination of eligibility. After reviewing the records in detail, 221 were excluded (220 did not treat patients with a cellular product and 1 trial was for compassionate use only and not a clinical trial). A total of 54 studies were included in our review (see Fig. 1). Study characteristics are summarized in Table 1 (see Table A.1. for a full list of included studies, Fig. A.1. for a timeline of all studies).

The most common cell type described in the planned studies was MSCs (41 studies, 76%), including 3 studies that will administer MSC-derived extracellular vesicles or “exosomes”, with a total of 1129 enrolled subjects projected to receive cells or cell-derived products (see Table A.2. for details). Amongst MSC studies, 27 (51%) describe a control group for comparison, with a combined projected enrollment of 801 patients to be treated with MSCs or MSC-derived products in a 1:1 (22 studies), 1:2 (4 studies), or 2:1 (1 study) ratio of controls to those in the intervention group. Controls were placebo (9 studies) or saline (7 studies) in a combined total of 16 studies that have a cumulative total

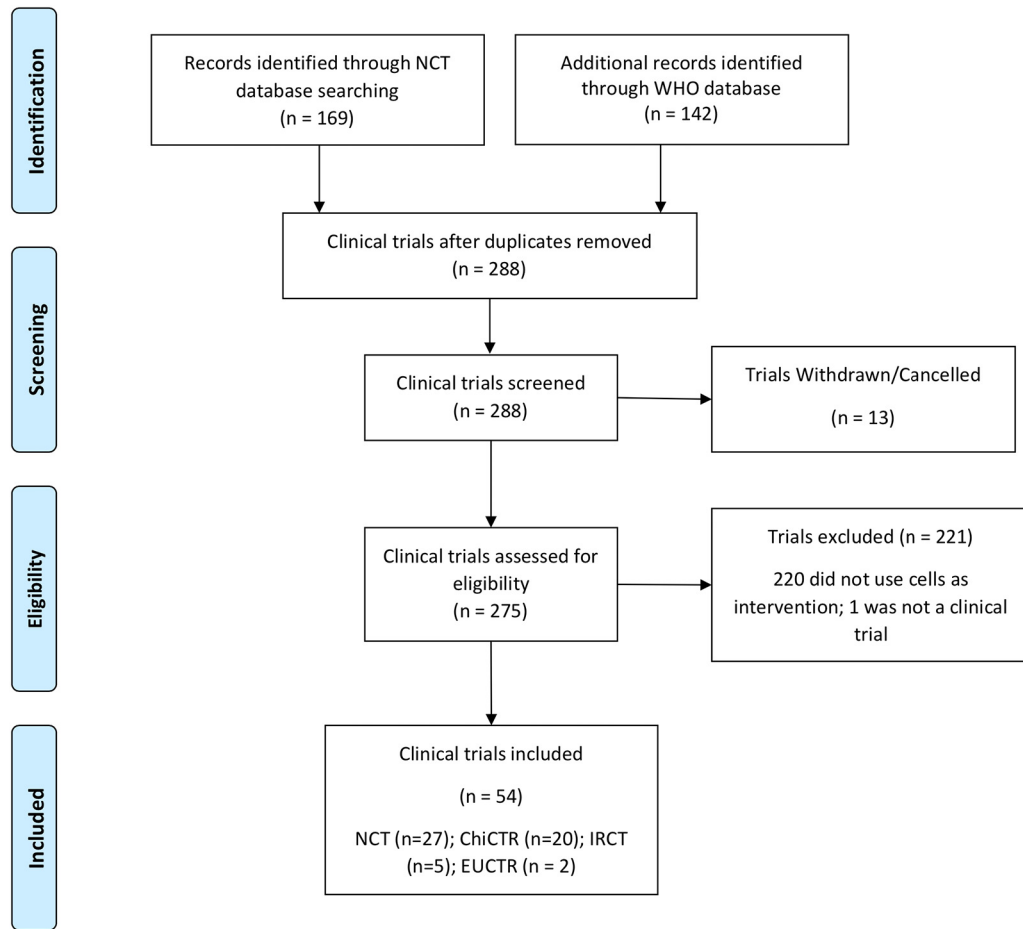


Fig. 1. Summary of search for registered trials of cellular therapy for COVID-19. NCT, clinicaltrials.gov; WHO, World Health Organization; ChiCTR, Chinese Clinical Trial Registry; IRCT, Iranian Registry of Clinical Trials; EUCTR, European Union Clinical Trials Register.

projected enrolment of 429 subjects in the intervention arms. The remaining studies describe a control group that will receive conventional therapy, standard of care, or was unspecified. With regards to potential risk of bias, we noted that while randomization was

described in 61% of studies, the method of randomization was not described for 39% of registered trials (see Table A.3.). Allocation concealment and blinding of assessors was described in 11% and 24% of the registered protocols.

Table 1
Summary of characteristics of all identified registered trials of cellular therapy for COVID-19

	Total trials (n = 54)		Controlled studies (n = 34)			
	Trials	Patients receiving cells	Trials	Patients receiving cells	Data collection to be completed by Dec 31, 2020 (trials) N = 23	Patients with data to be collected by Dec 31, 2020
Cell type						
MSC	41 ^{c,d}	1129	27	801	21	579
NK cells	5	135	3	35	2	25
Mononuclear cells	2 ^e	30	2	30	0	0
aAPC	1	100	0	0	0	0
Other ^a	6	172	3	43	1	10
Country						
China	35	1077	23	608	16	360
USA	6	188	4	102	2	87
Iran	5	66	2	45	2	45
Other ^b	8	225	5	144	3	112
Critical/severe Cases	17/31	459/778	10/18	254/432	5/12	164/322
Actively recruiting as of April 23, 2020	32	1108	19	622	14	462

MSC, Mesenchymal stem cell; NK cells, natural killer cells; aAPC, artificial antigen presenting cell. All patient numbers are based on projected enrolment; Some studies used more than one cell type/derived-product. If the study did not specify the sampling ratio, a 1:1 ratio was assumed per arm.

^a Other includes cytotoxic T-lymphocytes, cAStem, cellular stromal vascular fraction (cSVF), or unknown.

^b Other: Spain, UK, Jordan, Brazil, France, Denmark, Columbia.

^c Three studies used exosomes.

^d One study used extracellular vesicles.

^e One study used conditioned media.

With regards to MSC manufacturing, the starting cell source for MSC growth was placental tissue (18 studies, including umbilical cord or Wharton's jelly), adipose tissue in 7 studies, bone marrow (1 study) and unspecified or other in the remaining trials (15 studies) (see Table A.2.). Amongst studies with a placebo or saline control group, umbilical cord is the stated source for MSC expansion in 8 studies (50%). Additional manufacturing details such as conformance to recommendations by the International Society for Cellular Therapy for MSC characterization [11], use of xenogeneic products such as animal serum during cell culture, passage number and storage conditions of cells administered to patients and whether release criteria such as cell viability, product potency, or other criteria were used was generally unavailable from the information provided at registration. Amongst the controlled studies of MSCs, however, the severity of disease of patients to be enrolled was moderate to critical, with most analyzing severe cases [12,13].

The most commonly assessed outcomes amongst controlled MSC trials are safety and/or adverse events (primary in 12 [44%] trials, secondary in 4 [15%] trials), clinical response or clinical improvement (primary in 7 [26%] trials, secondary in 7 [26%]), radiographic findings (primary in 6 [22%] and secondary in 8 [30%] trials, serum inflammatory / immune markers (primary in 2 [7%] trials and secondary in 10 [37%] trials), oxygenation index (primary in 4 [15%] trials and secondary in 6 [22%] trials), and 28-day mortality (primary in 3 [11%] trials and secondary in 6 [22%] trials). These outcomes may represent the most promising candidates for pooling in future meta-analysis, although the extent to which supplemental data may be reported or could be obtained from investigators is not known.

Cell types other than MSCs are described in 14 (26%) registered trials of cellular therapy for COVID-19, including natural killer cells (5 trials) umbilical cord mononuclear cells (2 trials), pathogen-specific artificial antigen presenting (1 trial), immunity and matrix-regulatory cells (2 trials), pathogen-specific cytotoxic T-lymphocytes (1 trial), cellular stromal vascular fractions (1 trial), and unspecified cell types (2 trials). Non-MSc cell therapy trials have a combined total of 437 subjects that are projected to be enrolled, and 8 (57%) of these trials are controlled. Given the breadth of cell types and low cumulative enrolment on controlled studies, the extent to which these trials are suitable for pooling data and appropriate meta-analysis is uncertain.

We then estimated the required sample size required for different levels of significant reduction in key outcomes that could be determined through pooling of data from similar studies (See Table 2). Reported mortality rates for patients with severe COVID-19 are approximately 10–20% [14–16] and for critical disease, the reported mortality rates are 40–60% [14,16–20]. For clinically meaningful absolute reductions of 2–10% in mortality and other dichotomous outcomes, such as rates of intensive care unit (ICU) admission and need for mechanical ventilation, a cumulative sample size of 74 to 9493 subjects would be required for the intervention and control arms, depending on the outcome rate in the control arm (see Table 2). Based on the projected date of completion of registered controlled trials of MSC studies (see Fig. 2), we can expect sufficient numbers of patients to be enrolled by as early as September 2020 for an assessment of efficacy for at least some levels of projected improvement, depending on the mix of patients with severe and critical COVID-19.

Discussion

The number of newly registered cell-based studies to treat severe/critical COVID-19 is significant with many launching in early 2020 and many expected to complete data collection before or soon after the end of 2020. Many of the actively recruiting trials are studying the use of MSCs and enough are planning randomization with placebo or saline control groups that will make meta-analysis of similar studies feasible. The characterization and manufacturing details are lacking from the limited information available for most trials, but it is likely with efforts

Table 2

Required sample size needed to determine a significant absolute reduction in the proportion of study subjects experiencing a dichotomous outcome in the intervention group compared with a control group

Proportion in control outcome	Absolute % outcome reduction in intervention	n (intervention group) to detect delta, 1:1 enrolment
10%	2	4724
	5	686
	7.5	278
	10	74
20%	2	6039
	5	906
	7.5	379
	10	199
40%	2	9336
	5	1471
	7.5	644
	10	356
60%	2	9493
	5	1534
	7.5	686
	10	388
80%	2	6510
	5	1094
	7.5	505
	10	294

Outcomes are aligned with observed mortality rates for severe COVID-19 (10%-20%), critical COVID-19 (20%-60%) (13%-19), need for ICU admission (10%-20% of hospitalized patients), or for the need for mechanical ventilation amongst patients admitted to the ICU (20%-80%). Type I error = 0.05, Type II error = 0.2; two tailed comparison of proportions in independent groups (<https://www.stat.ubc.ca/~rollin/stats/ssize/b2.html>).

to standardize MSC characterization [11] and with more widespread use of similar manufacturing methods that this aspect of the study design may represent sufficient homogeneity to allow for pooling of data for meta-analysis. However, aspects of manufacturing MSCs that can impact cell function such as the manufacturing site, age of the donor, source of cells (whether umbilical cord, bone marrow or adipose tissue), and the extent of in-vitro expansion, amongst other variables may be anticipated as sources of heterogeneity [21,22]. Furthermore, storage conditions and release criteria prior to administration are also important, including cell viability and potency assays that can vary dramatically between published studies [21,23]. If these aforementioned factors are adequately reported upon publication of the results of these identified trials, it may be possible to account for these confounding factors with subgroup analyses.

The clinical aspects of study designs appear largely similar, including the definition of disease severity, ages and sex of eligible study participants, and while many studies report similar clinical outcomes such as mortality and rates of admission to ICU and the need for mechanical ventilation, this data may need to be requested from investigators of some studies to facilitate a framework for knowledge synthesis that relies on alignment of reported outcomes. Other surrogate markers of clinical response including radiographic responses, reverse transcriptase polymerase chain reaction results of virus levels, and measurement of inflammatory markers may be harder to combine depending on the timeframe for measuring these outcomes and specifics of the methods that will be used. A framework for sharing and obtaining supplemental data from studies on aligned outcomes will assist greatly with efforts to pool data and perform meaningful meta-analysis.

While blinding is not described for all studies, the use of objective outcomes may help to limit assessor bias. Moreover, randomization of subjects is described for many studies with a planned control group which limits allocation bias. Use of placebo or saline treatment instead of conventional or standard therapy as a control group will be important to control for the concomitant administration of other experimental therapies to these patients. Pooling data will increase power of these similar studies and allow for earlier understanding of efficacy. If

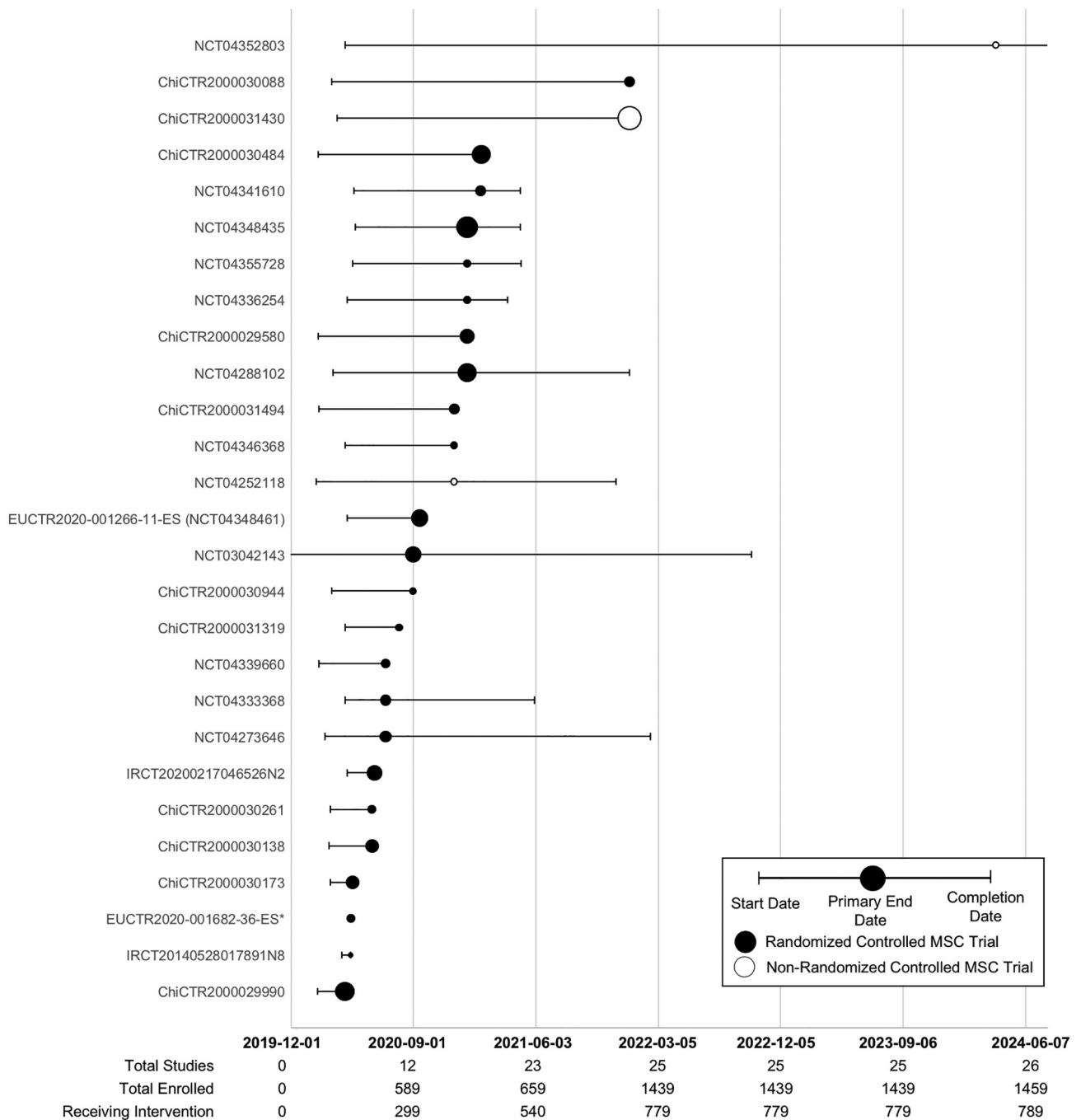


Fig. 2. Projected timeline registered controlled trials of mesenchymal stromal cell therapy for COVID-19 (n = 27) divided into randomized and non-randomized study designs. Y-axis lists the trial identification number; x-axis represents the date. The date of study completion may be same as primary end date. The size of the date of primary trial completion icon is proportional to the anticipated total enrolment. MSC, mesenchymal stem cell. *Only a start date was provided.

efficacious, regulatory bodies in affected countries could move more quickly to approve the class of MSC-based therapy, notwithstanding specific review of individual products regarding details related to production, storage, release of product and treatment parameters. It is important to acknowledge that some regulatory bodies, including the Food and Drug Administration in the United States and Health Canada in Canada have augmented efforts in recent months to curtail unproven use of stem cell therapies, underscoring the importance of a rigorous framework for assessment of novel applications of cellular therapy.

A framework for accelerated synthesis of trial evidence regarding MSCs to treat COVID-19 could facilitate the approval of a class of cellular therapy and allow investigators to prepare for more accelerated treatment of more patients using an approved therapy. The extent to

which this approach would be successful will depend on how studies are conducted and reported and on criteria established by regulatory bodies. Vigilant ongoing surveillance of treated patients would be necessary, of course, to continuously evaluate safety. In this way, the class of treatment could receive conditional approval, with ongoing surveillance data captured within a structured system. International cooperation and transparency would be important for the success of this proposed framework. MSCs have already been approved in Canada for the treatment of graft versus host disease following hematopoietic cell transplantation (Sanofi Genzyme), providing an existing framework for regulatory oversight of this cellular therapy.

It is possible that studies will not accrue patients at the rate anticipated. The incidence of severe COVID-19 disease will be difficult to

predict in the months ahead, especially since many studies are centered in China where the disease has slowed significantly in recent weeks [24]. The approach outlined in this proposed framework reduces bias as it would include all published data as soon as available, from studies that share sufficient similarity to be pooled and using criteria that are established in advance and registered on public registers. We have already registered a planned meta-analysis of MSC trials on PROSPERO, an international register of planned meta-analyses (protocol CRD42020181751; <https://www.crd.york.ac.uk/prospero/>) that will be conducted and reported in accordance with PRISMA guidelines [10]. As more study results become available, the meta-analysis would be updated to refine initial estimates regarding efficacy and to confirm rates of adverse events. Additional new trials are anticipated from new regions of the global research community which will expand the international reach of this proposed framework. It is also likely that some trials will be conducted and published that were never registered. This occurs more commonly with trials that are privately funded. While the lack of registration in advance may introduce potential bias in the reporting, results of trials that are not registered will also be considered for inclusion in our meta-analysis. We are aware of a few significant trials that are planned or ongoing that would fall in this category [25–28]. Additionally, our search criteria for this scoping review was limited to trials registered on or after December 1, 2019, we may have missed previously registered or ongoing cell-therapy trials for the treatment of ARDS that are now enrolling a COVID-19 specific cohort. Our meta-analysis strategy will expand the search restriction in order to capture those trials we may have missed.

In conclusion, our scoping review of registered clinical trials of cellular therapy for COVID-19 highlights an opportunity to perform rapid meta-analysis from placebo-controlled randomized controlled trials using MSCs which could be expanded to other cell types, to treat severe and critical cases. Sufficient power to detect important improvements in outcomes is anticipated by performing meta-analysis before the end of 2020. Accessing supplemental data from published studies on aligned and consistent objective outcomes will further accelerate knowledge synthesis efforts. Regulatory bodies should prepare for assessing pooled data using such a framework to evaluate possible applications for specific cellular therapies in this unique context.

Disclosures

No conflicts of interest to disclose.

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Author Statement

Gary Liao: Conceptualization, methodology, formal analysis, investigation, visualization, manuscript writing of original drafts, reviewing and editing. **Katina Zheng:** Conceptualization, methodology, formal

analysis, investigation, visualization, manuscript writing of original drafts, reviewing and editing. **Manoj Lahu:** Writing - Review & Editing, approval of final manuscript. **Dean S. Fergusson:** Methodology, Writing - Review & Editing, approval of final manuscript. **David Allan:** Conceptualization, methodology, project administration, visualization, manuscript writing, reviewing and editing, supervision.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.tmr.2020.06.001>.

References

- [1] Walker PGT, Whittaker C, Watson O, Baguelin M, Ainslie KEC, Bhatia S, et al. The global impact of COVID-19 and strategies for mitigation and suppression. *Imp Coll COVID-19 Response Team* 2020:1–19. [10.25561/77735](https://doi.org/10.25561/77735).
- [2] Ruan Q, Yang K, Wang W, Jiang L, Song J. Clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan. *China Intensive Care Med*. 2020. <https://doi.org/10.1007/s00134-020-05991-x>.
- [3] McIntyre LA, Moher D, Fergusson DA, Sullivan KJ, Mei SHJ, Lahu M, et al. Efficacy of mesenchymal stromal cell therapy for acute lung injury in preclinical animal models: a systematic review. *PLoS One*. 2016;11:1–16. <https://doi.org/10.1371/journal.pone.0147170>.
- [4] Lahu MM, Sullivan KJ, Mei SHJ, Moher D, Straus A, Fergusson DA, et al. Evaluating mesenchymal stem cell therapy for sepsis with preclinical meta-analyses prior to initiating a first-in-human trial. *Elife*. 2016;5:1–28. <https://doi.org/10.7554/eLife.17850>.
- [5] McIntyre LA, Stewart DJ, Mei SHJ, Courtman D, Watpool I, Granton J, et al. Cellular immunotherapy for septic shock: a phase I clinical trial. *Am J Respir Crit Care Med*. 2018;197:337–47. <https://doi.org/10.1164/rccm.201705-1006OC>.
- [6] Liang S, Jiao HL, Chi LK, Shi XY, Liang AM, Tian Y, et al. Clinical remission of a critically ill COVID-19 patient treated by human umbilical cord mesenchymal stem cells. *Chinese J Tissue Eng Res*. 2020;16:9179–85. <https://doi.org/10.3969/j.issn.2095-4344.2012.49.011>.
- [7] Leng Z, Zhu R, Hou W, Feng Y, Yang Y, Han Q, et al. Transplantation of ACE2-mesenchymal stem cells improves the outcome of patients with COVID-19 pneumonia. *Aging Dis*. 2020;11:216. <https://doi.org/10.14336/ad.2020.0228>.
- [8] Matthay MA, Calfee CS, Zhuo H, Thompson BT, Wilson JG, Levitt JE, et al. Treatment with allogeneic mesenchymal stromal cells for moderate to severe acute respiratory distress syndrome (START study): a randomised phase 2a safety trial. *Lancet Respir Med*. 2019;7:154–62. [https://doi.org/10.1016/S2213-2600\(18\)30418-1](https://doi.org/10.1016/S2213-2600(18)30418-1).
- [9] 2 Sample Non-Inferiority or Superiority Calculator. Power Sample Size 2020. <http://powerandsamplesize.com/Calculators/Compare-2-Proportions/2-Sample-Non-Inferiority-or-Superiority> (accessed April 4, 2020).
- [10] Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JPA, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. *BMJ*. 2009;339:b2700. <https://doi.org/10.1136/bmj.b2700>.
- [11] Dominici M, Le Blanc K, Mueller I, Slaper-Cortenbach I, Marini FC, Krause DS, et al. Minimal criteria for defining multipotent mesenchymal stromal cells. The International Society for Cellular Therapy position statement. *Cytotherapy*. 2006;8:315–7. <https://doi.org/10.1080/14653240600855905>.
- [12] Aylward, Bruce (WHO); Liang W (PRC). Report of the WHO-China Joint Mission on Coronavirus Disease 2019 (COVID-19). WHO-China Jt Mission Coronavirus Dis 2019 2020;2019:16–24.
- [13] Cheng ZJ, Shan J. 2019 novel coronavirus: where we are and what we know. *Infection*. 2020;48:155–63. <https://doi.org/10.1007/s15010-020-01401-y>.
- [14] Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet*. 2020;395:1054–62. [https://doi.org/10.1016/S0140-6736\(20\)30566-3](https://doi.org/10.1016/S0140-6736(20)30566-3).
- [15] Guan W, Ni Z, Hu Y, Liang W, Ou C, He J, et al. Clinical characteristics of coronavirus disease 2019 in China. *N Engl J Med*. 2020. <https://doi.org/10.1056/NEJMoa2002032>.
- [16] Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet*. 2020;395:497–506. [https://doi.org/10.1016/S0140-6736\(20\)30183-5](https://doi.org/10.1016/S0140-6736(20)30183-5).
- [17] Arentz M, Yim E, Klaff L, Lokhandwala S, Riedo FX, Chong M, et al. Characteristics and outcomes of 21 critically ill patients with COVID-19 in Washington state. *JAMA*. 2020. <https://doi.org/10.1001/jama.2020.4326>.
- [18] Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. *JAMA*. 2020;323:1061–9. <https://doi.org/10.1001/jama.2020.1585>.
- [19] Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72 314 cases from the Chinese Center for Disease Control and Prevention. *JAMA*. 2020. <https://doi.org/10.1001/jama.2020.2648>.
- [20] Yang X, Yu Y, Xu J, Shu H, Xia J, Liu H, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. *Lancet Respir Med*. 2020. [https://doi.org/10.1016/S2213-2600\(20\)30079-5](https://doi.org/10.1016/S2213-2600(20)30079-5).
- [21] Rizk M, Monaghan M, Shorr R, Kekre N, Bredeson CN, Allan DS. Heterogeneity in studies of mesenchymal stromal cells to treat or prevent graft-versus-host disease:

- a scoping review of the evidence. *Biol Blood Marrow Transplant*. 2016;22:1416–23. <https://doi.org/10.1016/j.bbmt.2016.04.010>.
- [22] Liu S, de Castro LF, Jin P, Civini S, Ren J, Reems J-A, et al. Manufacturing differences affect human bone marrow stromal cell characteristics and function: comparison of production methods and products from multiple centers. *Sci Rep*. 2017;7:46731. <https://doi.org/10.1038/srep46731>.
- [23] Galipeau J. The mesenchymal stromal cells dilemma—does a negative phase III trial of random donor mesenchymal stromal cells in steroid-resistant graft-versus-host disease represent a death knell or a bump in the road? *Cytotherapy*. 2013;15:2–8. <https://doi.org/10.1016/j.jcyt.2012.10.002>.
- [24] Bhatia S, Cori A, Parag KV, Ainslie KEC, Baguelin M, Bhatt S, et al. Forecast 1–07 April 2020. MRC Centre for Global Infectious Disease Analysis. <https://www.imperial.ac.uk/mrc-global-infectious-disease-analysis/covid-19/covid-19-weekly-forecasts/forecast-1-covid-19-week-07-04-2020/>. [Accessed 13 May 2020].
- [25] Therapeutics Pluristem. Coronavirus Disease – COVID-19. Pluristem; 2020 <https://www.pluristem.com/coronavirus-disease-covid-19/>. [Accessed 17 June 2020].
- [26] Cynata Therapeutics Limited. Cynata Receives Ethics Approval to Commence Clinical Trial in COVID-19 and Clinical Development Update. GlobeNewswire; 2020 <https://www.globenewswire.com/news-release/2020/05/08/2030332/0/en/Cynata-Receives-Ethics-Approval-to-Commence-Clinical-Trial-in-COVID-19-and-Clinical-Development-Update.html>. [Accessed 17 June 2020].
- [27] Athersys Inc. Athersys announces commencement of patient enrollment in the MACOVIA study, a pivotal phase 2/3 trial evaluating MultiStem® cell therapy for COVID-19 induced ARDS. Athersys Inc. <https://www.athersys.com/investors/press-releases/press-release-details/2020/Athersys-Announces-Commencement-of-Patient-Enrollment-in-the-MACOVIA-Study-a-Pivotal-Phase-23-Trial-Evaluating-MultiStem-Cell-Therapy-for-COVID-19-Induced-ARDS/default.aspx>; 2020. [Accessed 17 June 2020].
- [28] Mesoblast Limited. First patients dosed in phase 2/3 randomized controlled trial of Mesoblast's Remestemcel-L for COVID-19 acute respiratory distress syndrome. Globe Newswire n.d. <https://www.globenewswire.com/news-release/2020/05/06/2028234/0/en/First-Patients-Dosed-in-Phase-2-3-Randomized-Controlled-Trial-of-Mesoblast-s-Remestemcel-L-for-COVID-19-Acute-Respiratory-Distress-Syndrome.html>.