

COMMENTS AND OPINIONS

Use of the Estimand Framework to Manage the Disruptive Effects of COVID-19 on Stroke Clinical Trials

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ABSTRACT: The coronavirus disease 2019 (COVID-19) pandemic has presented unique challenges to stroke care and research internationally. In particular, clinical trials in stroke are vulnerable to the impacts of the pandemic at multiple stages, including design, recruitment, intervention, follow-up, and interpretation of outcomes. A carefully considered approach is required to ensure the appropriate conduct of stroke trials during the pandemic and to maintain patient and participant safety. This has been recently addressed by the International Council for Harmonisation which, in November 2019, released an addendum to the Statistical Principles for Clinical Trials guidelines entitled Estimands and Sensitivity Analysis in Clinical Trials. In this article, we present the International Council for Harmonisation estimand framework for the design and conduct of clinical trials, with a specific focus on its application to stroke clinical trials. This framework aims to align the clinical and scientific objectives of a trial with its design and end points. It also encourages the prospective consideration of potential postrandomization intercurrent events which may occur during a trial and either impact the ability to measure an end point or its interpretation. We describe the different categories of such events and the proposed strategies for dealing with them, specifically focusing on the COVID-19 pandemic as a source of intercurrent events. We also describe potential practical impacts posed by the COVID-19 pandemic on trials, health systems, study groups, and participants, all of which should be carefully reviewed by investigators to ensure an adequate practical and statistical strategy is in place to protect trial integrity. We provide examples of the implementation of the estimand framework within hypothetical stroke trials in intracerebral hemorrhage and stroke recovery. While the focus of this article is on COVID-19 impacts, the strategies and principles proposed are well suited for other potential events or issues, which may impact clinical trials in the field of stroke.

Key Words: clinical trial ■ coronavirus ■ pandemics ■ randomized controlled trial ■ stroke ■ stroke rehabilitation

Well-designed and implemented randomized controlled clinical trials have produced a number of transformative changes in stroke management over the past 3 decades and will be required for the development of the next generation of novel stroke treatments. In 2020, the severe acute respiratory syndrome coronavirus 2 (coronavirus disease 2019 [COVID-19]) pandemic presented major challenges in global health care delivery, including the appropriate delivery of stroke care.¹ These challenges continue at crisis levels in many countries around the world. The global pandemic also poses specific challenges in the conduct of randomized controlled clinical trials in stroke and other areas of health care. Specific to stroke, the interruption of usual

acute stroke assessment, management and rehabilitation pathways, potential biological interactions between COVID-19 and stroke, unpredictability of government restrictions and responses, and general disruption of health and other services including study monitoring and pharmaceutical supply chains are just some of the potential COVID-19 related issues which may jeopardize stroke trial integrity, validity, and interpretation.

Although not exclusively a disease of aging, stroke tends to affect older people with multiple medical comorbidities. Unsurprisingly, a past history of stroke has been shown to be independently associated with in-hospital mortality following COVID-19 infection.² A common sentiment of most national frameworks for the conduct of

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Nonstandard Abbreviations and Acronyms

COVID-19	coronavirus disease 2019
ICH	International Council for Harmonisation

clinical trials during the COVID-19 pandemic has been the need to balance the priority of participant and community safety with the importance of ongoing medical research, both related to COVID-19 as well as in other important health conditions, such as stroke.³⁻⁵ Research conducted during the pandemic must also maintain the appropriate standards and adhere to local regulatory requirements and good clinical practice, although many jurisdictions have introduced some flexibility and pragmatism into these processes including allowances for remote consent and recruitment, remote study monitoring, and telehealth consultations.

Stroke clinical trials span the spectrum of stroke care from primary and secondary prevention, to hyperacute medical care, to rehabilitation. Study interventions can include medical therapies, device-based interventions, and nonpharmacological behavioral interventions. Stroke trial outcome measures also vary widely and can include clinical end points such as stroke incidence or recurrence, surrogate imaging or biomarker end points which are particularly useful in phase II studies, and functional end points, which may include the widely used modified Rankin Scale or more targeted measures, such as the Fugl Meyer Assessment for upper and lower limb motor impairment. While it has limitations, the widespread use of the modified Rankin Scale is likely to be an advantage during COVID-19 given its ease of administration, validity in the setting of telephone⁶ and telehealth⁷ administration, and ability to derive the score from medical records.⁸ Nonetheless, the wide variety of trial objectives, designs, interventions, and outcomes means that the potential impacts of the COVID-19 pandemic on stroke trial integrity are complex and unique to each individual trial. While some trials may be relatively resilient to the impacts of COVID-19 (eg, hyperacute trials where a primary end point is assessed very early after stroke onset), other trials may be more vulnerable (eg, recovery trials that deliver the intervention over multiple days or weeks in the hospital, rehabilitation, or community environment).

In this article, we discuss a framework for understanding potential COVID-19 impacts on clinical trials within the field of stroke and propose principles and practices to support investigators to develop contingency strategies to deal with these impacts. In particular, we discuss the estimand framework, as outlined in a recent addendum to the International Council for Harmonisation (ICH) guidelines on Statistical Principles for Clinical Trials.^{9,10} We discuss the implications of the estimand approach for the field of stroke, and its implementation

within stroke trials, which we would recommend as a cornerstone of the contingency strategy for COVID-19. This approach is also a more broadly applicable strategy to ensure the proper planning, conduct and interpretation of stroke clinical trials in the face of other potential disruptive factors.

SEARCH STRATEGY

We searched MEDLINE and Embase for articles published between January 1, 2015, and December 31, 2021. We used the search term “Estimand” and identified 221 unique articles. We then searched MEDLINE and Embase for the terms “Stroke” AND “Estimand” and identified a single abstract which did not relate the estimand framework. We reviewed guidance documents published by the ICH on clinical trial design and conduct and the estimand framework. We provide this personal view based on the resulting narrative review of the literature.

COVID-19 AND STROKE TRIALS

The potential impacts of COVID-19 on stroke trials are varied. The pandemic may impact the study population of interest on many levels. For example, in many jurisdictions, patients with stroke have been reluctant or unable to seek acute medical care due to hospitals being overwhelmed with COVID-19.¹¹ This could affect the distribution of stroke severity observed in stroke trials during the pandemic, potentially leading to the unplanned exclusion of less severe stroke patients. In addition, patients with stroke may be reluctant to participate in clinical trials which require in-person intervention and assessment at health services due to the risk of exposure to COVID-19. The biological interactions between COVID-19 and stroke may also confound the natural history of stroke or the interpretation of treatment response in a trial. For example, several reports have described an increase in thromboembolic events in patients with COVID-19, which could affect trials interested in stroke outcome, incidence, or recurrence.¹² At a health-systems level, COVID-19 related closures or disruptions may lead to an inability to maintain active study assessments and procedures, which may lead to the initial randomized study population being different to the final study population.

In addition to the study population, COVID-19 can also affect study outcome measures. Apart from effects on functional or surrogate outcomes as a direct result of COVID-19 infection, COVID-19 restrictions may prevent the collection of an outcome in the study if a patient is unable to be assessed (and the outcome is not able to be obtained through remote assessment or telehealth). This is particularly challenging where the primary end point in the study is a continuous outcome or change in

a particular variable from baseline, in which case such an end point would be impossible to report.

Finally, COVID-19 related events can simultaneously have major practical implications on both individual study participants and on the overall conduct of the trial (eg, site closures or interruption of investigational product supply chain).

Given the complexity of these issues, a carefully considered framework is required to adequately prepare clinical trials and ensure that they remain as resilient as possible to the impacts of the pandemic, as well as other factors which may interfere with the trial. For many years, a number of national and international regulatory bodies have provided such guidance frameworks on good clinical practice and conduct of clinical trials. In the area of pharmaceuticals, the ICH of Technical Requirements for Pharmaceutical for Human Use has provided internationally accepted and implemented principles and practices for the conduct of clinical trials and general development strategies for medicinal products.¹³ The ICH also released a framework for the Statistical Principles for Clinical Trials in 1998.⁹ In November 2019, the ICH released an addendum to the Statistical Principles Guidelines on Estimands and Sensitivity Analysis in Clinical Trials.¹⁰ While this addendum was not released in direct response to the COVID-19 pandemic, it was fortuitously timed as it provides a response and framework of design and analysis strategies to deal with COVID-19 related impacts on clinical trials. In addition to this, other national and international bodies, including the United States Food and Drug Administration, the European Medicines Association, and the National Health and Medical Research Council of Australia, have provided guidance documents on the management of clinical trials during the COVID-19 pandemic.^{3–5,14}

THE ESTIMAND FRAMEWORK

The estimand framework is a set of design and analysis principles which broadly aim to improve clinical trial planning and interpretation by aligning the overall objective of the study with the study design and end points and by prespecifying strategies for dealing with various external or internal events which may occur during the study. The framework is ideally suited to providing a statistical contingency strategy for COVID-19 in clinical trials, including trials across the spectrum of stroke care. The estimand framework relies on the careful definition of 4 principal concepts:

1. Target study population (eg, patients with ischemic stroke within 4.5 hours of onset who have large vessel occlusion). This target population should be clearly defined by the inclusion and exclusion criteria in the study protocol.
2. Individual-level end point of interest (eg, modified Thrombolysis in Cerebral Infarction-2B or greater)

3. Population-level summary of variable (eg, proportion of participants with Thrombolysis in Cerebral Infarction-2B or greater in each group)
4. Intercurrent events: These are events occurring after treatment initiation that affect either the interpretation or the existence of the measurement associated with the clinical question of interest.¹⁰ (eg, COVID-19 infection or changes to a participant's other medications)

Each of these concepts represents a potential area of vulnerability for the trial and, therefore, requires careful consideration and definition.

INTERCURRENT EVENTS

A specific discussion of the concept of intercurrent events is warranted here given these have not been traditionally considered in stroke trials. A prespecified and careful assessment of potential intercurrent events is a key component of the estimand framework. The types of intercurrent events that are likely to occur in a trial are often predictable and mirror clinical practice. Careful consideration of potential intercurrent events can, therefore, allow for the appropriate interpretation and translation of a clinical trial outcome.

A clear distinction should also be made between the concept of missing data and intercurrent events. For example, while both participant withdrawal and a terminal event such as death during a trial can lead to an inability to record a primary outcome measure (missingness of this variable), the interpretation of these 2 events is clearly different.

Missing data due to subject withdrawal, loss to follow-up, or clerical and administrative issues are a potential drawback for a clinical trial and should generally be avoided. Under ideal circumstances, such data could have been collected and their interpretation would have been no different to that of actually collected data (Figure 1). However, intercurrent events affect the ability to collect or interpret an outcome even under ideal circumstances of trial protocol adherence.

Two distinct categories of intercurrent events can be conceptualized:

- Events affecting the ability to measure an outcome (ie, resulting in an outcome that does not exist due to the intercurrent event, eg, measurement of infarct growth in a participant who died before follow-up time point)
- Events affecting the interpretation of a measured outcome

Figure 1 provides an overview of the concepts of collectability and interpretability of outcome data to distinguish between missing data and intercurrent event categories. The potential for occurrence of intercurrent events that may affect the integrity and validity of a trial calls for predefined strategies for dealing with such

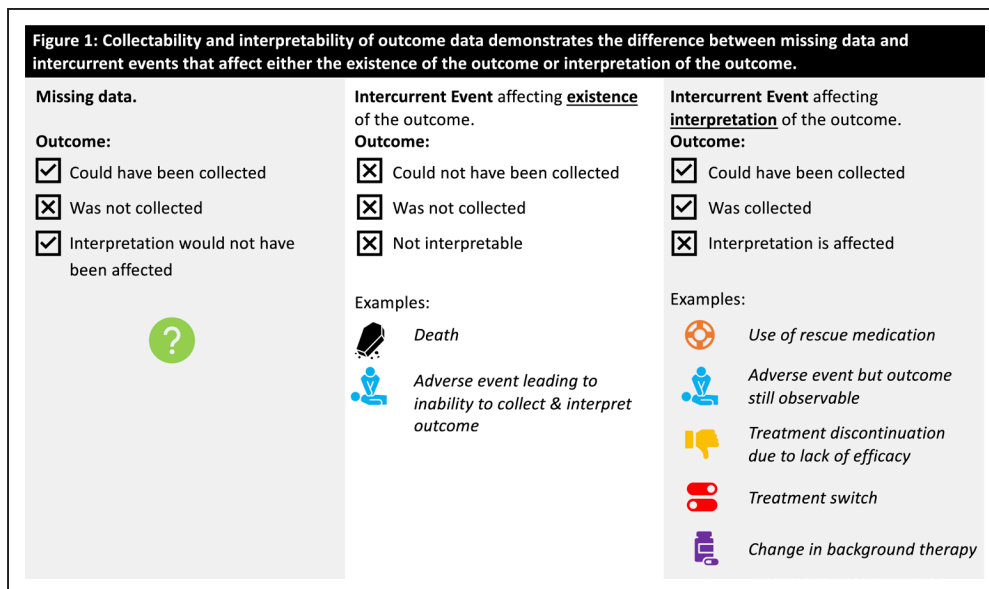


Figure 1. Collectability and interpretability of outcome data demonstrate the difference between missing data and intercurrent events that affect either the existence of the outcome or interpretation of the outcome.

events. For each intercurrent event, a number of different strategies may be available, and the precise choice of the optimal strategy depends on the category of the intercurrent event as well as the overall clinical and scientific objectives of the trial.

STRATEGIES FOR DEALING WITH INTERCURRENT EVENTS

The estimand framework requires a clear and unambiguous predefinition of the proposed strategies for dealing with intercurrent events. Figure 2 provides an overview of such strategies. The potential strategies are briefly described below and examples which may be relevant to stroke trials are provided.

1. **Treatment policy strategy:** A treatment policy strategy uses the measured value of an outcome regardless of the presence or absence of any intercurrent events. This strategy essentially considers any intercurrent events (eg, medication changes) as a part of the treatments being compared in the trial. This strategy has the most parallels in its approach to the intention to treat principle. Importantly, however, use of this strategy requires confidence that the outcome can be measured regardless of any intercurrent event which may occur, which may not be the case for some terminal events (eg, a trial using a brain imaging end point would not be able to measure the end point if the intercurrent event of mortality occurred before measurement).
2. **Hypothetical strategy:** A hypothetical strategy is one in which it is possible to impute a hypothetical outcome which assumes an intercurrent event had not occurred. For example, in a stroke recovery trial where upper

limb function is measured longitudinally, a hypothetical strategy may specify that if the intercurrent event of COVID-19 infection occurs, some appropriately chosen summary measure will be imputed based on the performance of participants who did not develop COVID-19 infection. Caution should be advised when using this strategy, with particular attention required to ensure that this hypothetically generated outcome is clinical meaningful and realistic.

3. **Composite strategy:** A composite strategy allows for the occurrence of a specific intercurrent event to potentially alter the outcome variable. The use of this strategy is dependent on the outcome variable and is particularly useful for dichotomous end points. For example, in a study where the primary outcome measure is a binary good outcome versus bad outcome, a good outcome may be defined as only occurring if the participant achieves a particular threshold on a functional scale and the intercurrent event of treatment cessation does not occur. This strategy can also be applied to ordinal outcomes (such as the modified Rankin Scale) where investigators may choose to apply the worst possible outcome on an ordinal scale in the case of a particular intercurrent event. While the composite strategy can be used for measures with a clearly defined worst outcome (a common feature of constructed scales such as the National Institutes of Health Stroke Scale, with the worst-case score of 42), it is generally not applicable for outcome variables where such values do not exist naturally. This is often the case with physiological measures (eg, blood pressure, glucose, and blood biomarker concentrations), thus leading to difficulties in using a composite strategy for such outcomes.

Figure 2: Five strategies and how they can be applied to intercurrent events (IE) that affect the outcome.		
Strategies	Intercurrent Event affecting existence of the outcome. Outcome: <input checked="" type="checkbox"/> Could not have been collected <input checked="" type="checkbox"/> Was not collected <input checked="" type="checkbox"/> Not interpretable	Intercurrent Event affecting interpretation of the outcome. Outcome: <input checked="" type="checkbox"/> Could have been collected <input checked="" type="checkbox"/> Was collected <input checked="" type="checkbox"/> Interpretation is affected
Treatment policy strategy: Data collected for the outcome are used regardless of whether or not IE occurs	<input checked="" type="checkbox"/> <i>Cannot be implemented as outcome values after the IE do not exist for all participants</i>	<input checked="" type="checkbox"/>
Composite strategy: IE is integrated with one or more other measures into a composite outcome	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>
Hypothetical strategy: A hypothetical scenario without IE is applied	<input checked="" type="checkbox"/> <i>The outcome cannot be observed but can be predicted/imputed</i>	<input checked="" type="checkbox"/> <i>The outcome cannot be observed but can be predicted/imputed</i>
Principal stratum strategy: Outcome estimated only within strata defined by occurrence or absence of an IE (defined prior to trial commencement)	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>
While on treatment strategy: Outcome measured prior to occurrence of IE	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>

Figure 2. Five strategies and how they can be applied to intercurrent events (IE) that affect the outcome.

4. While on treatment strategy: This strategy allows for the use of an outcome variable before the occurrence of a defined intercurrent event rather than at the specified assessment time points. While the title of the strategy implies treatment, the strategy can apply to a variety of scenarios such as while alive. For example, a clinical trial may obtain repeated measures at set intervals of a particular clinical or functional end point and may be particularly interested in the value of the measure while the participant is alive, or before the occurrence of a particular clinical event (eg, change in concurrent medication). The while on treatment strategy allows for the use of the last value of the outcome measure before the occurrence of the intercurrent event.
5. Principal stratum strategy: This strategy refines the definition of the population of interest by the occurrence or absence of an intercurrent event prespecified before randomization. If the clinical question is relevant only within a particular subgroup (principal stratum) of patients, this strategy is particularly useful. For example, a clinical trial may only be interested in measuring a particular outcome of interest in participants who survive until the last study assessment, complete the entire intervention protocol, or in whom a recurrent stroke has not occurred.

framework can be used to provide a statistical contingency strategy within stroke research trials. Each hypothetical trial presents different intercurrent events (eg, COVID-19 infection, use of a rescue medication or death) that occur before collection of the primary or secondary trial end points to illustrate different strategies within the estimand framework. The acute stroke trial demonstrates a single strategy for a single intercurrent event (Figure 3B), as well as how 2 different strategies may be used for a single intercurrent event (Figure 3C). This is important to consider as an intercurrent event may be addressed via different strategies and selection of the most appropriate strategy for a given trial depends on the overall clinical and scientific objectives of the trial. In the recovery example, we similarly demonstrate how a single strategy may be used for a single intercurrent event (Figure 4B) and illustrate how >1 intercurrent event and >1 strategy can be used for the same outcome (Figure 4C). This reflects that multiple intercurrent events may occur and a combination of strategies may be required to optimally implement the estimand framework.

PRACTICAL CONSIDERATIONS

While the estimand framework provides important design and analysis considerations and strategies for the conduct of clinical trials, the implementation of this framework also generally identifies a number of practical and operational challenges which must be managed in parallel. The COVID-19 pandemic can have practical impacts on subject enrollment, treatment discontinuation, compliance/missed doses or intervention sessions, change in concurrent medications, data collection, and errors or protocol deviations.¹⁵ The general operational strategy for dealing with the pandemic will initially depend on the

ILLUSTRATIVE EXAMPLE APPLICATIONS OF ESTIMAND FRAMEWORK TO STROKE TRIALS

We now present a hypothetical hyperacute stroke (Figure 3A through 3C) and acute stroke recovery trial (Figure 4A through 4C) to illustrate how the estimand

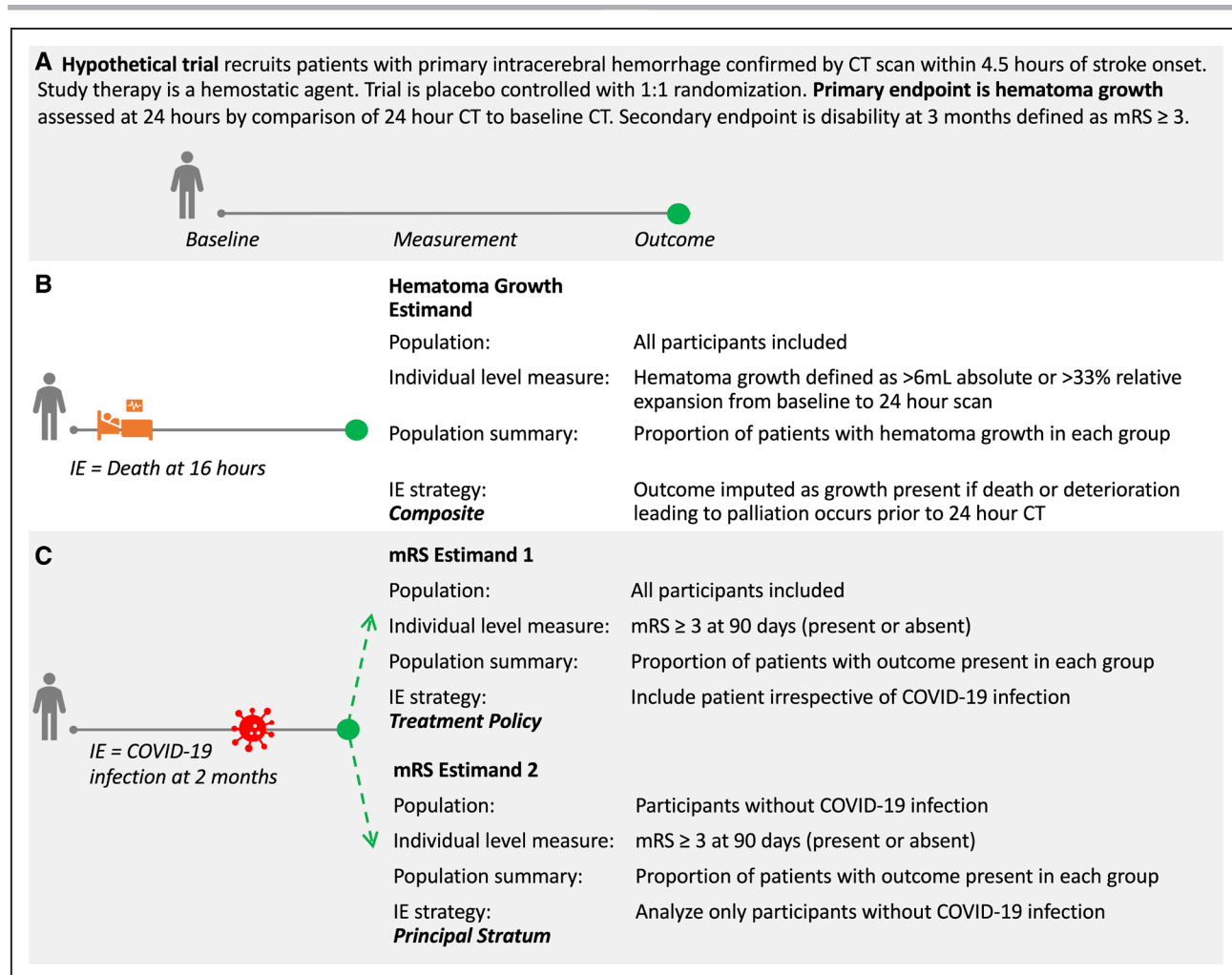


Figure 3. Application of the estimand framework to a hypothetical acute stroke trial.

A, Trial overview and design. **B**, Illustration of a single strategy applied to an intercurrent event (IE). **C**, Illustration of how 2 different strategies may be applied to a single IE. COVID-19 indicates coronavirus disease 2019; CT, computed tomography; and mRS, modified Rankin Scale.

progress of the trial to date. Trials that have not commenced recruitment are in some respects advantaged by the opportunity to place temporary holds on recruitment, especially if the trial location is in the midst of a surge of COVID-19, or to take the opportunity to make key improvements to safe-guard the trial design before commencement. This requires a careful discussion between the trial funding body, sponsor, Institutional Review Board, and investigator team.

Clinical trials that were ongoing at the beginning of the pandemic are generally more susceptible to the impacts of the pandemic. However, even these trials may be variably affected depending on the focus and original design of the trial. For example, many centers have continued to provide acute ischemic stroke thrombolysis and endovascular thrombectomy throughout the pandemic, and studies in these hyperacute fields may be able to maintain active recruitment and observation of participants during their inpatient stay. Many such studies also involve only slight variations from standard care and are able to continue despite stretched workforces during the

pandemic (eg, studies comparing 2 alternative thrombolytics or thrombectomy approaches). Studies where the primary end point is collected early (eg, studies where the primary end point is angiographic reperfusion) are particularly advantaged by this. However, even such studies generally involve a delayed (eg, 3 or 6 months) end point, and the ability to collect the commonly used trial end point of the modified Rankin Scale over the telephone is a key advantage in the stroke field.

Other studies, particularly those in the subacute phase of stroke or in the area of stroke recovery face the additional challenge of recruitment within rehabilitation facilities which may have been repurposed for COVID-19 care, or where implementation of therapies which are outside standard care may not be feasible due to workforce or resource limitations. Such studies also face the challenge of often requiring close contact between the patient and therapist to deliver care, and many require return to a center for in-person intervention and evaluation for the determination of the primary outcome, both of which may increase the risk of transmission.

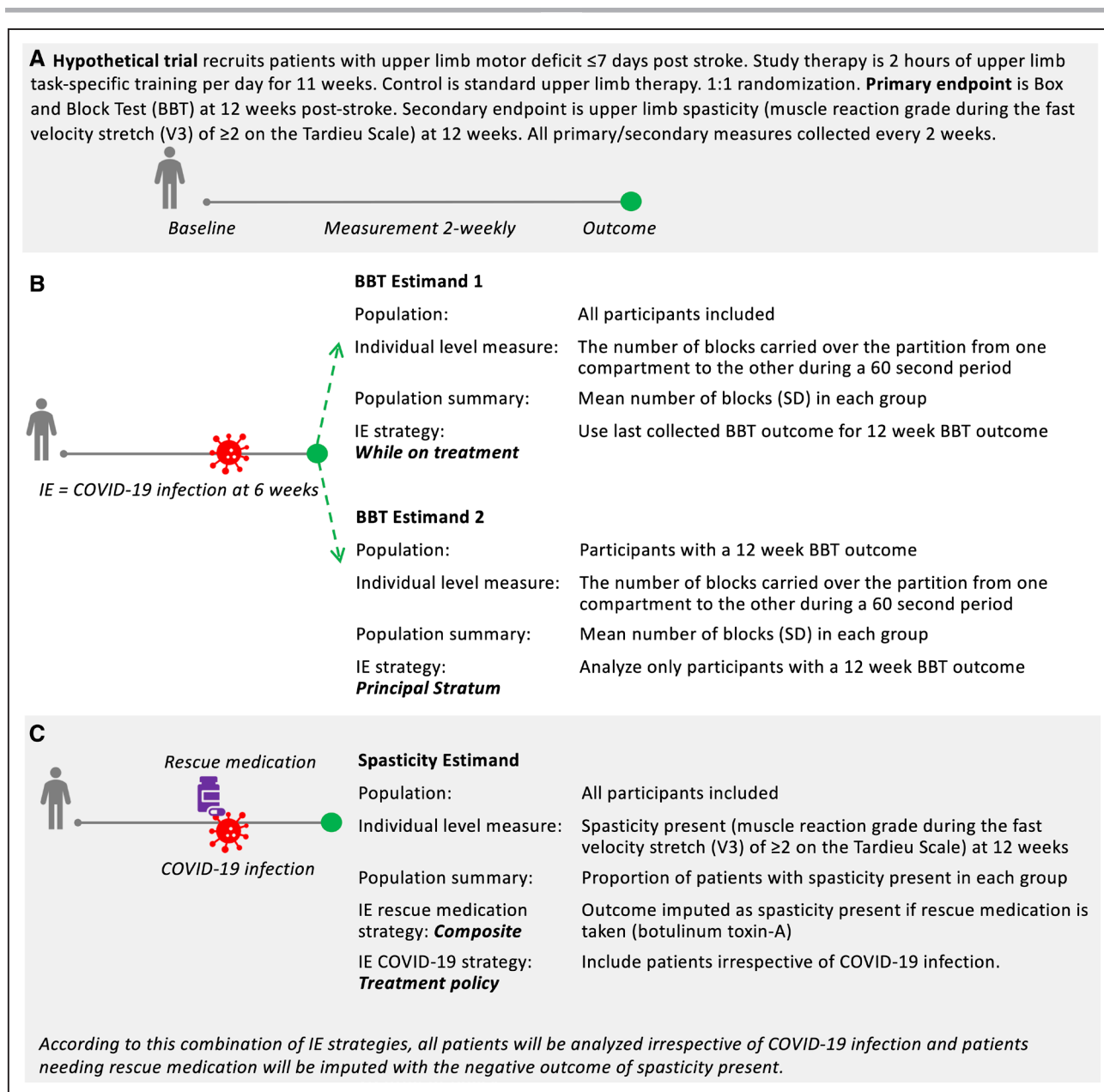


Figure 4. Application of the estimand framework to a hypothetical upper limb motor recovery trial.

A, Trial overview and design. **B**, Illustration of how 2 different strategies may be applied to an intercurrent event (IE). **C**, Illustration of how >1 IE and >1 strategy can be used for the same outcome. COVID-19 indicates coronavirus disease 2019.

All stroke trials are also potentially confounded by the biological interaction between stroke and COVID-19. Early during the pandemic, a hypercoagulable state was described as part of COVID-19 infection,¹² and an excess of severe stroke was described in communities with a significant burden of COVID-19 infection.^{16–19} In studies where incident or recurrent stroke is either an efficacy or safety end point, such an interaction may act as a serious confounder, and may affect the interpretation of the trial results. This is particularly important for primary and secondary prevention stroke trials.

Based on careful review of the trial protocol, investigators should prespecify the practical strategies which

will be adopted to mitigate the potential impact of the pandemic on the trial. A list of potential practical considerations has been proposed by other authors and, while not necessarily comprehensive, these provide a useful starting point and can be readily adopted to the field of stroke.¹⁵ We have generally categorized these as follows, noting that overlap between the categories is common:

- Factors related to suspected or confirmed COVID-19 infection: Trials should prespecify how participants who undergo testing for suspected COVID-19 will be managed within the trial considering the required infection control and quarantine measures. Plans for confirmed COVID-19

infection are also required. These may include plans to account for the risk of missed outcome assessments as a result of COVID-19 infection, potential cessation of study drugs due to safety concerns or commencement of other concomitant medications (eg, anticoagulant therapy) in the setting of COVID-19 infection.

- Factors related to the logistic impacts of COVID-19: Impacts of quarantine and travel limitations should be considered both at the individual level as well as at the broader level of the trial operations (eg, ability to perform safety monitoring or overall trial monitoring). Potential impacts of site closures should be considered, which can lead to stopped enrollment, delayed or missed interventions or assessments. Alternative measures for collection of data and specimen may be required in such cases. COVID-19 impacts on transport and logistics may also lead to interruption to supply chains of an investigational product or participant's other medications.

Based on these principles, we recommend that stroke trials be designed and redesigned to include 2 additional sections in the trial protocol:

1. An estimand section—Rethinking Outcomes as Estimands.
2. A COVID-19 impact statement—Prespecifying the trial's contingency plan for different COVID-19-related impacts.

In our experience, such proactive changes to trial protocols have been met with very strong support by Institutional Review Boards, sponsors, and funding bodies.

CONCLUSIONS AND FUTURE DIRECTIONS

In response to the COVID-19 pandemic, and based on a growing body of clinical trial methodology literature and industry guidelines outlining best-practice principles, stroke research must rapidly adapt its approach to the design and conduct of clinical trials. In this article, we have outlined the general principles of the ICH estimand framework, the primary objective of which is to carefully align the objectives of a clinical trial with its design and to prospectively plan for potential events which may impact the collection or interpretation of outcome. In addition, we have outlined advice on practical steps which can be taken by research groups to protect clinical trials from the potentially disruptive impacts of COVID-19 on its participants or the locations in which the trial is being performed. Our conclusions are aligned with several international recommendations, including recommendations from the ICH, and demonstrate an evidence-informed approach to the use of the estimand framework in stroke trials. While the focus has been on impacts due

to COVID-19, these principles and practices are equally suited to plan for other potential issues which may impact proper conduct and interpretation of clinical trials across the continuum of stroke care.

ARTICLE INFORMATION

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