Protocol for Deferral of Consent in Acute Stroke Trials

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Abstract

The challenges of conducting hyperacute stroke research and obtaining informed consent have been increasingly recognized within the stroke research community in recent years. Deferral of consent, in which a patient is enrolled in a trial and then provides consent at some point thereafter, is increasingly used to enroll patients into hyperacute stroke trials in Canada and Europe, although it is not permitted in the United States. Deferral of consent offers several potential advantages—quicker door-to-randomization, increased enrolment, decreased selection bias—but these must be balanced against the risk of enrolling patients against their wishes. We seek to minimize the attendant risks of deferral of consent by offering practical guidance regarding how to conduct acute stroke trials using deferral of consent. Building on existing guidelines and recent experiences with deferral of consent in acute stroke trials, we have developed a protocol for the use of deferral of consent that aims to maximize patient involvement while minimizing ethical and scientific risks.

Introduction

The challenges of conducting hyperacute stroke research and obtaining informed consent have been increasingly recognized within the stroke research community in recent years. Deferral of consent, in which a patient is enrolled in a trial before providing informed consent, is increasingly used to enroll patients into hyperacute stroke trials in Canada and Europe, but it is not permitted in the United States. Deferral of consent offers several potential advantages over prospective informed consent, including limiting the bias that can be introduced when only capable patients are enrolled into stroke trials. Other potential benefits include increasing trial enrollment, shortening the length of time required to complete trials, and potentially reducing door-to-randomization times, although these are not proven. However, deferral of consent carries certain ethical risks, primarily the possibility that patients are being enrolled into trials against their wishes. We believe that protocolizing the way deferral of consent is implemented in acute stroke trials might minimize these risks. Therefore, in designing the Alteplase Compared to Tenecteplase (AcT) trial, we built on existing guidelines and recent experiences in acute stroke trials to develop a protocol for deferral of consent that aims to maximize patient involvement and minimize ethical and scientific risks. In this article, we will review the available literature surrounding deferral of consent for acute stroke trials to contextualize the deferral of consent protocol that we developed for the AcT trial.

Informed Consent and Its Variations

Informed consent is central to modern medical research, consistent with the principle of respect for persons. Informed consent is a process in which a potential research participant provides permission to be enrolled in a study. In the context of a randomized clinical trial, potential trial participants should be informed of the aims of the trial, the methods,
procedures, risks, potential benefits, alternatives to participation, plans for use of personal and private information, and discontinuation options. To provide informed consent before randomization, a person must have decisional capacity, be free of coercion, be informed with adequate information, and not rushed. These conditions rarely apply to patients with acute stroke: patients with stroke frequently lack decisional capacity because of their neurologic impairments, and the full disclosure imagined in traditional regulations is not practical, given the time limitations of acute stroke treatment. Kompanje et al. have proposed a more detailed characterization of the prerequisites for informed consent in their recent consideration of the challenges of obtaining informed consent for patients with neurologic emergencies. Moreover, studies of patients with stroke who have provided informed consent demonstrate that they frequently lacked a clear understanding of the purpose or principles of the trials in which they participated.

A commonly used alternative to informed consent is surrogate or proxy consent, where a substitute decision maker (a family member, relative, or legal representative) provides consent to treatment or trial participation on behalf of the patient. In the context of stroke, the short therapeutic window for acute treatment and difficulty contacting surrogates limit the practicability of surrogate consent. The COVID-19 pandemic has only exacerbated these challenges because of restricted hospital access. Furthermore, the surrogate is not guaranteed to make a choice commensurate with the patient’s preferences if there have not been previous discussions between the surrogate and patient. A study involving hypothetical surrogate decision-making found that surrogates predicted patient preferences around trial participation approximately half the time, depending on the scenario. In most cases where there was disagreement, patients would have desired to participate in a trial, but surrogates would have refused on their behalf.

When informed consent and surrogate consent are not possible, deferral of consent may be used. Under deferral of consent, an eligible patient is enrolled without prospective consent, but consent for further participation in the trial is sought as soon as the patient regains capacity or a surrogate becomes available. Deferral of consent may be called “waiver of consent” in some jurisdictions, although this terminology is best reserved for studies where there is no attempt to gain consent at all. In situations where it is impossible to obtain informed or surrogate consent, deferral of consent may be the only way for that person to participate in the trial. The main motivations for the use of deferred consent are to prevent delays in treatment, to increase enrollment, to allow for people who could not consent to participate, and to increase data validity and quality. In one critical care study, a significant treatment effect became nonsignificant when patients enrolled with deferral of consent were excluded. Deferral of consent is frequently used in emergency medicine research and has increasingly been used in stroke trials over the last decade.

Deferral of consent is controversial, in that its use has the potential to enroll patients into trials who would have objected, had they been able to express themselves. Some critics argue that deferral of consent could be a slippery slope toward “unilateral paternalistic decision making by trial investigators while eroding patient autonomy.” These concerns have become more prominent with the use of deferral of consent in clinical trials during the COVID-19 pandemic. Given the serious concerns regarding the use of deferral of consent, regulatory guidelines govern when it can be implemented, although these vary according to the jurisdiction.

A final alternative to standard informed consent would be to use advance consent, in which patients at risk of stroke (such as those attending a stroke prevention clinic) could provide consent for participation in a trial should they have a stroke in the future. This process would be the closest approximation of true informed consent at the time of the stroke but has not yet been assessed in a real-world context for patients eligible for enrollment into acute stroke trials.

Guidelines for Deferral of Consent: Canada, the United States, and the European Union

Multiple sets of guidelines exist to regulate consent practices in research, with foundational principles first outlined in
the World Medical Association’s Declaration of Helsinki (1964). There are many different approaches to regulating departures from informed consent. American guidelines focus on the concept of “ Exceptions from Informed Consent (EFIC),” which generally refers to a full waiver of consent. Deferral of consent is not a recognized approach under American guidelines. In contrast, Canadian and UK guidelines emphasize the concept of deferral of consent, whereas European guidelines incorporate both waiver of consent and deferral of consent approaches.

Canadian, American, and European guidelines have many broad similarities regarding alterations to standard informed consent (Table). All 3 guidelines require that participation offers a realistic possibility of direct benefit to the participant, implying that the use of deferral of consent should be reserved for phase III trials of treatments that could be effective. Early phase studies (e.g., with novel agents that have not been tested in humans) would not be appropriate for deferral of consent. Generally speaking, deferral (or waiver) of consent is considered acceptable when the participant lacks the capacity to provide informed consent and it is infeasible to obtain surrogate consent within the required time frame. It is only in emergency situations—which are frequently prohibitive for finding a surrogate decision-maker—that deferred consent is appropriate. In instances where there is no time pressure, deferral should not be used. In addition, regulations specify that a potential participant’s previous wishes must be followed, that informed consent for continued participation must be obtained at the soonest opportunity, and that ethics review is required.

There are key differences between existing guidelines. Although American guidelines require community consultation before launching a trial using an exception from informed consent, Canadian guidelines only recommend doing so. Canadian and American guidelines specify that there be a documented and diligent effort to obtain surrogate consent, whereas European guidelines do not make this stipulation. It is important to note that American guidelines of “EFIC” allow either informed consent, surrogate consent, or waiver of consent, in which no consent is sought; deferral of consent is not a recognized option.

Other than in the protocol we propose, no particular advice for a data and safety monitoring board (DSMB) has been included in existing guidelines related to deferral of consent. Patient withdrawals from studies in which they were enrolled by deferral of consent are likely to be an important marker of the acceptability of deferral of consent. Setting a prespecified threshold for concern would be reasonable, although there has been no empirical work as of yet to determine what that threshold should be. Furthermore, although there are no patient populations that explicitly cannot be recruited by deferral of consent, we acknowledge that research should be conducted in a way that is sensitive to vulnerable groups. Special consideration should be given to circumstances where there is particular concern about the possibility of coercion, such as in cases where patients are incarcerated.

Recent Experiences With Deferral of Consent in Stroke Trials

Deferral of consent is becoming increasingly common in acute stroke trials. A review of 36 acute stroke trials published between 2010 and 2014 identified 9 trials that recruited by means other than standard informed consent. In the 8 years since, many more trials have used deferral of consent, including as the exclusive method of enrollment, as in AcT, Solitaire With the Intention for Thrombectomy Plus Intravenous tPA vs DIRECT Solitaire Stent-Retriever Thrombectomy in Acute Anterior Circulation Stroke (SWIFT-DIRECT), Ultra Early Tranexamic Acid After Subarachnoid Hemorrhage (ULTRA), and others. Despite its frequent use in recent stroke trials, trial protocols have not offered a standardized approach to justifying the use of deferral, meaning they have not explicitly stated why it was required. In their review, Feldman et al. identified mentions of the presence of research ethics board approval (as in Hyperacute Stroke Alarm Study, International Stroke Trial 3 [IST-3], Local vs Systemic Thrombolysis for Acute Ischemic Stroke-Expansion), of the need for rapid treatment (as in Intensive vs Subcutaneous Insulin in Patients With Hyperacute Stroke, Paramedic Initiated Lisinopril for Acute Stroke Treatment), of the right of patients to not have alteplase withheld (Prehospital Transdermal Glycerol Trinitrate in Patients with Ultra-Acute Presumed Stroke), and of the ability of clinical professionals to provide surrogate consent (Prehospital Transdermal Glycerol Trinitrate in Patients with Ultra-Acute Presumed Stroke). Endovascular Treatment for Small Core and Anterior Circulation Proximal Occlusion with Emphasis on Minimizing CT to Recanalization Times (ESCAPE) and A Phase 3, Global, Multi-Center, Double-Blind, Randomized, Efficacy Study of Zolbetuximab (IMAB362) Plus mFOLFOX6 Compared With Placebo Plus mFOLFOX6 as First-line Treatment of Subjects With Claudin (CLDN)18.2-Positive, HER2-Negative, Locally Advanced Unresectable or Metastatic Gastric or Gastroesophageal Junction (GEJ) Adenocarcinoma (SPOTLIGHT) made explicit statements of justification, citing the potential to increase enrollment and enable study participation for more severely affected patients. While it is clear that deferral of consent permits the inclusion of patients with more severe strokes, it is not clear that deferral shortens time to randomization or otherwise increases enrollment. Although enrollment by deferral of consent was associated with a significant difference in door-to-randomization times in the International Stroke Trial 3 trial, no such difference was observed in the ESCAPE trial. Feldman et al. found that there was no clear association between recruitment rates and the use of alternatives to written informed consent.
Table: Regulation of Deferral of Consent

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<td><strong>Immediate threat</strong></td>
<td>—</td>
<td>a. Serious threat to the prospective participant requires immediate intervention.</td>
<td>(1) The human subjects are in a life-threatening situation, available treatments are unproven or unsatisfactory...</td>
<td>Clinical trial relates directly to the life-threatening or debilitating medical condition from which the subject suffers.</td>
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<td><strong>RCT required</strong></td>
<td>—</td>
<td>—</td>
<td>(1) … and the collection of valid scientific evidence, which may include evidence obtained through randomized placebo-controlled investigations, is necessary to determine the safety and effectiveness of particular interventions.</td>
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<td><strong>Possibility of benefit</strong></td>
<td>This group should stand to benefit from the knowledge, practices or interventions that result from the research.</td>
<td>b. Either no standard efficacious care exists, or the research offers a realistic possibility of direct benefit to the participant in comparison with standard care.</td>
<td>(3) Participation in the research holds out the prospect of direct benefit to the subjects because: (i) Subjects are facing a life-threatening situation that necessitates intervention; (ii) Appropriate animal and other preclinical studies have been conducted, and the information derived from those studies and related evidence support the potential for the intervention to provide a direct benefit to the individual subjects; and</td>
<td>There are scientific grounds for expecting that participation in the clinical trial will produce: (1) A direct benefit to the incapacitated subject outweighing the risks and burdens involved.</td>
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<td><strong>Justifiable Risk</strong></td>
<td>Medical research involving human subjects may only be conducted if the importance of the objective outweighs the risks and burdens to the research subjects.</td>
<td>c. Either the risk is not greater than that involved in standard efficacious care, or it is clearly justified by the prospect for direct benefits to the participant.</td>
<td>(3) (iii) Risks associated with the investigation are reasonable in relation to what is known about the medical condition of the potential class of subjects, the risks and benefits of standard therapy, if any, and what is known about the risks and benefits of the proposed intervention or activity.</td>
<td>Trial will pose only minimal risk to, and will impose minimal burden on, the incapacitated subject concerned in comparison with the standard treatment of the incapacitated subject's condition.</td>
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<td><strong>Lack of capacity</strong></td>
<td>Research involving subjects who are physically or mentally incapable of giving consent (e.g., unconscious patients), may be done only if the physical or mental condition that pre-vents giving informed consent is a necessary characteristic of the research group.</td>
<td>d. The prospective participant is unconscious or lacks capacity to understand the risks, methods and purposes of the research project.</td>
<td>(2) Obtaining informed consent is not feasible because: (i) The subjects will not be able to give their informed consent as a result of their medical condition; and</td>
<td>The clinical trial is essential with respect to incapacitated subjects.</td>
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<td><strong>Surrogate consent not feasible</strong></td>
<td>If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee.</td>
<td>e. Third party authorization cannot be secured in sufficient time, despite diligent and documented efforts to do so.</td>
<td>(2) (ii) The intervention under investigation must be administered before consent from the subjects’ legally authorized representatives is feasible.</td>
<td>The clinical trial is essential with respect to incapacitated subjects and data of comparable validity cannot be obtained in clinical trials on persons able to give informed consent.</td>
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<td><strong>No prior wishes</strong></td>
<td>—</td>
<td>f. No relevant prior directive by the participant is known to exist.</td>
<td>(2) (iii) There is no reasonable way to identify prospectively the individuals likely to become eligible for participation in the clinical investigation.</td>
<td>The explicit wish of an incapacitated subject who is capable of forming an opinion and assessing the information referred to in Article 29(2) to refuse participation in, or to withdraw from, the clinical trial at any time, is respected by the investigator.</td>
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### Table: Regulation of Deferral of Consent (continued)

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<td>Inform and consent upon regained capacity or at the earliest opportunity</td>
<td>Consent to remain in the research must be obtained as soon as possible from the subject or a legally authorized representative. When a previously incapacitated participant regains decision-making capacity, or when an authorized third party is found, consent shall be sought for continuation in the project, and for subsequent examinations or tests related to the research project.</td>
<td>7 (b) The IRB is responsible for ensuring that procedures are in place to inform, at the earliest feasible opportunity, each subject, or if the subject remains incapacitated, a legally authorized representative of the subject, or if such a representative is not reasonably available, a family member, of the subject’s inclusion in the clinical investigation, the details of the investigation and other information contained in the informed consent document. The IRB shall also ensure that there is a procedure to inform the subject, or if the subject remains incapacitated, a legally authorized representative of the subject, or if such a representative is not reasonably available, a family member, that he or she may discontinue the subject’s participation at any time without penalty or loss of benefits to which the subject is otherwise entitled. If a legally authorized representative or family member is told about the clinical investigation and the subject’s condition improves, the subject is also to be informed as soon as feasible. If a subject is entered into a clinical investigation with waived consent and the subject dies before a legally authorized representative or family member can be contacted, information about the clinical investigation is to be provided to the subject’s legally authorized representative or family member, if feasible.</td>
<td>The subject shall as far as possible take part in the informed consent procedure.</td>
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<td>Waiver of consent required</td>
<td>Research cannot be carried out in a nonvulnerable group.</td>
<td>(4) The clinical investigation could not practicably be carried out without the waiver.</td>
<td>The clinical trial is essential with respect to incapacitated subjects and data of comparable validity cannot be obtained in clinical trials on persons able to give informed consent, or by other research methods.</td>
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<td>Ethics review required</td>
<td>The study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Local research ethics boards are required to approve the protocol.</td>
<td>(6) The IRB has reviewed and approved informed consent procedures and an informed consent document consistent with §50.25. These procedures and the informed consent document are to be used with subjects or their legally authorized representatives in situations where use of such procedures and documents is feasible. The IRB has reviewed and approved procedures and information to be used when providing an opportunity for a family member to object to a subject’s participation in the clinical investigation consistent with paragraph (a) 7 (v) of this section.</td>
<td>A clinical trial shall be subject to scientific and ethical review and shall be authorised in accordance with this Regulation. The ethical review shall be performed by an ethics committee in accordance with the law of the Member State concerned.</td>
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The attitudes of the general public and trial participants toward the use of deferral of consent is also mixed. A review of American and Canadian surveys of trial participants found that the public largely supports the use of waivers or deferral of consent for emergency research.32 One survey of stroke survivors indicated 92% support for research using EFIC,33 although only 55% of respondents in a different survey would participate in a hypothetical stroke study with deferred consent.34 More than 90% of participants surveyed after the ESCAPE trial disagreed with the use of deferred consent in the ESCAPE trial, with more than 78% disagreeing with its use for stroke trials in general.10 However, in the SPOTLIGHT trial, 9 of 10 surveyed substitute decision-makers agreed or strongly agreed with the use of deferred consent.19 Conversely, 92% of patients or proxies and 70% of physicians surveyed agreed with the use of deferred consent in the ULTRA trial for acute stroke, with willingness to participate in future studies remaining the same or increased in 94% of surveyed patients or proxies.35 Regardless of attitudes toward the deferral of consent, in both the ESCAPE and SPOTLIGHT trials, none of the participants enrolled by deferral of consent withdrew from the study.19

### How to Apply Deferral of Consent: A 6-Step Operationalized Approach

Current regulations governing the use of deferral of consent are regionally specific and do not contain direction on how to conduct a trial using deferral of consent.

In light of recent experiences with trials such as ESCAPE and SPOTLIGHT, we sought to develop a protocol for implementing deferral of consent that could serve as a set of best practices to be followed while still meeting standards for ethics review.19

Beginning from ethical first principles and recent scholarship,24,36 and extending through an iterative process involving stroke trialists, patient partners, and research ethics experts, we designed a protocol for deferral of consent and implemented it in the AcT trial. AcT is the first trial that we are aware of to follow a specific protocol for the use of deferral of consent. In designing the protocol, we sought to establish practices that would be synchronous with national guidelines, ensure close ethical oversight to minimize ethical risks, and maximize patient engagement at every step of the research process.19

### Table Regulation of Deferral of Consent (continued)

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<td>Community consultation</td>
<td>It may be appropriate to consult family members or community leaders.32</td>
<td>7 (i) Consultation (including, where appropriate, consultation carried out by the IRB) with representatives of the communities in which the clinical investigation will be conducted and from which the subjects will be drawn; (ii) Public disclosure to the communities in which the clinical investigation will be conducted and from which the subjects will be drawn, prior to initiation of the clinical investigation, of plans for the investigation and its risks and expected benefits; (iii) Public disclosure of sufficient information following completion of the clinical investigation to apprise the community and researchers of the study, including the demographic characteristics of the research population, and its results;</td>
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<td>Independent oversight</td>
<td>The research protocol must be submitted for consideration, comment, guidance and approval to the concerned research ethics committee before the study begins. This committee must be transparent in its functioning, must be independent of the researcher, the sponsor and any other undue influence and must be duly qualified.34</td>
<td>7 (iv) Establishment of an independent data monitoring committee to exercise oversight of the clinical investigation In order to allow for independent control as to whether these principles are adhered to, a clinical trial should be subject to prior authorization.</td>
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Abbreviations: IRB = institutional review board
Step 1: Designate an ethics lead, whose responsibilities include ensuring that the trial complies with ethical standards and mediating potential conflicts between research and therapeutic obligations.

Designating an ethics lead vests a member of the trial team with the authority to deal with ethical responsibilities and defines what those responsibilities may be. Many of the guidelines for deferral consent, such as community consultation requirements, are poorly defined and inconsistently interpreted by researchers and Institutional Review Boards. An ethics lead would make sure that rules are followed, patients are involved in decision-making, and that the ethical risks of the trial are minimized.

Step 2: Involve people with lived experience in trial planning and include a patient representative on the trial steering committee. Patient partners are incorporated into trial oversight and are more directly involved than when community consultation is depended on to reflect their input. This practice both allows researchers to liaise with a key stakeholder group and may lead to trial designs that will ultimately be more acceptable to patients, thereby increasing satisfaction and preventing future withdrawals. By taking a more focused approach and working with the existing patient population in the design of the study, this step goes beyond simply informing the community, a practice recognized to be of limited utility.

Step 3: Publish the justification of, and trial protocol for, deferral of consent to ensure that its use is transparent, consistent, and peer-reviewed. Considering the potential ethical pitfalls of using deferral of consent, all trials should publish a justification—meaning why it is necessary—and a trial protocol outlining how it will be used. This would ensure transparency and allow for peer review.

The use of deferral of consent should be assessed within an ethical framework such as the substitute consent model proposed by Largent et al. or the model we have proposed. It is important to determine participant attitudes toward deferral of consent because perspectives on its use are mixed. These assessments are feasible to do because they have previously been performed in ESCAPE, SPOTLIGHT, AcT, SWIFT-DIRECT, NICE-SUGAR, ULTRA, and many others. Divergent survey results such as seen in ESCAPE demonstrate the importance of continuing to gather this information. Gaining a better understanding of how patients feel about the use of deferral of consent through surveys or more formal qualitative studies will help researchers to continue to improve consent procedures in future stroke trials.

Step 6: Determine participant attitudes toward deferral of consent by surveying or interviewing patients once they regain capacity or their proxies if capacity is not regained. Although withdrawal of patients enrolled by deferral of consent is rare, monitoring patient withdrawals and reporting to the appropriate authorities will allow problems and concerns to be identified, investigated, and addressed in an expedient manner. Prespecifying the acceptability thresholds for patient withdrawals, and reviewing reasons given for patients withdrawals, would be vital to monitoring the progress and safety of the trial by an oversight committee or DSMF. If a trial were to have withdrawals exceeding the acceptability threshold (e.g., greater than 3%–5%), additional review would be warranted.

It is important to determine participant attitudes toward deferral of consent because perspectives on its use are mixed. These assessments are feasible to do because they have previously been performed in ESCAPE, SPOTLIGHT, AcT, SWIFT-DIRECT, NICE-SUGAR, ULTRA, and many others. Divergent survey results such as seen in ESCAPE demonstrate the importance of continuing to gather this information. Gaining a better understanding of how patients feel about the use of deferral of consent through surveys or more formal qualitative studies will help researchers to continue to improve consent procedures in future stroke trials.

Conclusion

As deferral of consent becomes an increasingly recognized practice in acute stroke trials, it will be critical to understand the technical and ethical consequences of its use. Given the differences in national guidelines for the implementation of deferral of consent, we sought to develop a 6-step approach that addresses the fundamental principles underlying existing guidelines, with an eye toward maximizing both ethical oversight and patient engagement. By following practices such as these in trials such as AcT, we can better determine the benefits, limitations, and attitudes of stakeholders surrounding the use of deferral of consent. These data will be essential to inform the design of future clinical trials in acute stroke and other emergency conditions.

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