Spotlight on Consent: Lessons from the SPOTLIGHT Trial for Acute Intracerebral Hemorrhage

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Abstract

Background SPOTLIGHT was a Canadian multicentre, placebo-controlled, randomized trial of emergency treatment with recombinant Factor VIIa for patients with acute intracerebral hemorrhage that enrolled a subset of eligible patients via deferral of consent. We investigated attitudes towards deferral of consent among participants and their legally-authorized representatives (LARs).

Methods All participants or LARs approached for enrolment in SPOTLIGHT were invited to complete an 11-item questionnaire within the first 4 days of enrolment, and again at 90 days.

Results Eight out of 50 participants in SPOTLIGHT (16%) were enrolled via deferral of consent. Ten LARs for participants (20%) completed the initial survey and 6 completed the 90 day follow-up survey. Ninety percent of respondents agreed with the process of deferral of consent both in principle and specifically for the SPOTLIGHT trial. Participants were more likely to support deferral of consent for low-risk or time-sensitive interventions, or in situations with no alternative treatment options.

Conclusions The majority of respondents were supportive of using deferral of consent to enrol participants into SPOTLIGHT and acute stroke trials.

Introduction

National and international regulations reflect the importance of informed consent in clinical research, but many also acknowledge that alternate strategies may be employed in emergency situations. In hyperacute stroke research, most patients lack capacity to provide consent due to their deficits, such as aphasia, neglect, or unconsciousness. The exclusion of patients who lack capacity from participation in stroke research is problematic, in that it discriminates against them due to their illness, introduces selection bias, and affects the generalizability of study results. In these scenarios, various approaches have been adopted. In Canada and in many other jurisdictions, a legally authorized representative (LAR) is typically sought to provide surrogate consent, though an LAR is not always identified quickly enough to enable enrollment for trials of highly time-sensitive interventions. Elsewhere, only a legally appointed guardian, or a two-physician consent process, may be used to enroll patients who lack capacity into emergency research.

For these reasons, some research studies have been conducted allowing for the enrolment of patients via deferral of consent (where enrollment happens without consent, and patients are asked to consent to ongoing participation once capable). Although used in the landmark ESCAPE trial and in the ongoing SWIFT DIRECT trial, deferral of consent remains controversial in acute stroke trials: many jurisdictions do not allow it, and recent results suggest that stroke patients are uncomfortable with it. We sought to investigate the attitudes of patients and their LARs towards deferral of consent in the “Spot Sign Selection of Intracerebral Hemorrhage to Guide Hemostatic Therapy” (SPOTLIGHT) study.

Methods

SPOTLIGHT was a randomized, double-blind study of recombinant activated factor VII vs. placebo as an emergency treatment for patients with life-threatening intracerebral hemorrhage (ICH). The overall study methods and results have been published. Capable patients, patients accompanied by a LAR, or patients whose LAR could be reached by telephone, were enrolled through a two-stage consent process: reviewing and signing a brief assent document, followed by a full consent process after enrolment. Incapable patients without an available LAR could be enrolled by a process of deferral of consent, where approved by the participating site's research ethics board, and with confirmation from a second physician of the patient's eligibility and incapacity. The explicit objective of this process was to allow for rapid administration of a time-sensitive treatment.

As a sub-study of SPOTLIGHT, the decision-makers approached to provide initial assent or ongoing consent — be it the participants themselves or their LARs — were invited to complete an 11 question structured telephone interview. This work was approved by the local REB and consent to participate was gained by both patients and their LARs, where applicable. Even those approached for the trial who declined enrollment were eligible to complete the survey. Questions were focused on opinions surrounding deferral of consent in general, and specifically for the SPOTLIGHT trial. Interviews were administered by telephone within the first 4 days by one blinded independent investigator (MS), not involved in the patient`s clinical care or study enrolment. The same participants were invited to answer an identical questionnaire at 90 days (Appendix 1), again by telephone with the same investigator.

Results

Local research ethics boards at 7 of the 14 participating SPOTLIGHT sites, all in Canada, approved the deferral of consent process for this trial. Of 50 patients enrolled in SPOTLIGHT, 8 patients (16%) from 5 sites were enrolled by deferral of consent. None of the participants from the deferral group withdrew from the study.

There were no significant differences in either time to treatment or outcome between the standard consent and deferral of consent groups.

Ten decision-makers completed the initial interview (Table 1), all of whom were LARs for enrolled patients. Six completed the 90-day follow up interview. Three of the patients whose LARs responded to this survey had been enrolled via deferral of consent.

Table 1
Baseline characteristics of interview participants.

Total number of participants, n	**10**
Male, n (%)	8 (80)
Age range (years), n (%)	
18–30	1 (10)
31–40	1 (10)
41–50	1 (10)
51–60	5 (50)
61–70	1 (10)
71–80	0 (0)
>80	1 (10)
Race and ethnicity	
Caucasian	6 (60)
Black	1 (10)
Asian	3 (30)
Education	
High school	3 (30)
University or college	6 (60)
Post-graduate	1 (10)
Enrolment method	
Standard	7 (70)
Deferral of consent	3 (30)

Nine of ten LARs agreed or strongly agreed with the process of deferral of consent in principle. They agreed that deferral was more or most appropriate if the study intervention was felt to carry low risk (9/10), if there were no alternative treatments available (9/10) and if the treatment needed to be administered quickly for greatest efficacy (8/10). Nine of ten agreed or strongly agreed with the use of a deferral for SPOTLIGHT. This pattern was maintained at 90 days. The LARs for all three patients who had been enrolled by deferral of consent agreed or strongly agreed with deferral of consent in principle and for SPOTLIGHT.

When asked about their reasons for consenting to participate, all 10 respondents agreed or strongly agreed that they preferred the therapeutic option available in the trial and that their trust in the physician was a factor. One participant stated that “we have to take a chance and allow doctors to do their studies to help patients.” Only one respondent wished not to make the decision about consent, and two endorsed wanting the doctor to decide.

When asked to recall basic elements of the consent document such as inclusion criteria and what the study drug was expected to do, comprehension was mixed, both at baseline and at 90-days (Fig. 1).

Discussion

Many prior studies have demonstrated that patients are generally supportive of enrollment into RCTs via deferral of consent, particularly in life-threatening situations.[1] However, the first published study to ask acute stroke trial participants about their attitudes towards deferred consent found that respondents were overwhelmingly opposed.[3] What could account for the discrepancy between that response, and those of SPOTLIGHT participants? The literature suggests that the severity of illness and type of experimental intervention (low vs. high risk) are important factors, though both acute ischemic stroke and ICH are severe conditions whose treatments are potentially risky. Another possibility, supported by SPOTLIGHT responses, is that the lack of any existing approved or effective treatment for acute ICH made enrollment by deferral of consent more acceptable. One respondent specifically stated that all enrolled patients should “get the treatment.”

While the majority of SPOTLIGHT respondents supported deferral of consent, they also felt that patient-participants should still be included in the consenting process. These results should encourage acute stroke trialists to develop novel ways of engaging with patients about research participation, potentially through a process of advanced consent in which individuals at risk of stroke or ICH are asked to provide broad consent should they ever become candidates for RCT enrollment. The development of a clinical-research infrastructure that allows for ultra-early drug administration is likely to be the future of acute ICH trials. Pairing such a system with the use of advanced consent could support the goal of rapid treatment, while also respecting patients’ choices about research participation.

The main limitation of the present study is its small sample size, reflecting both the small size of SPOTLIGHT (50 patients), and a low response rate (20%) for this substudy. This problem further supports the importance of innovation around enrollment techniques for acute stroke RCTs. Moreover, the generalizability of our results could be affected by the inherent limitations of questionnaire-based studies, including non-response bias. The questionnaire was not pre-validated in ICH patients, though only LARs responded. Moreover, the accuracy of responses were comparable to those obtained in prior studies involving participants with stroke or other conditions.

Declarations

Ethics Approval and Consent to Participate:

Ethics approval was gained through the Sunnybrook Health Sciences Centre Research Ethics Board, Toronto, Ontario. Consent to participate was gained by the patients or, when unable to provide consent, by their legally authorized representatives.

Consent for Publication:

Not applicable.

Availability of Data and Materials:

Data will be made available upon request.

Competing Interests:

The authors declare no competing interests.

Authors' Contributions:

MS and DG conceived of the project and MS acquired the data. TF and MS interpreted the data and drafted the work. BD, AD, MH, MF, and DG substantively revised the work. All authors have approved the submitted version and agree to be personally accountable for the content of the study.

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Figures

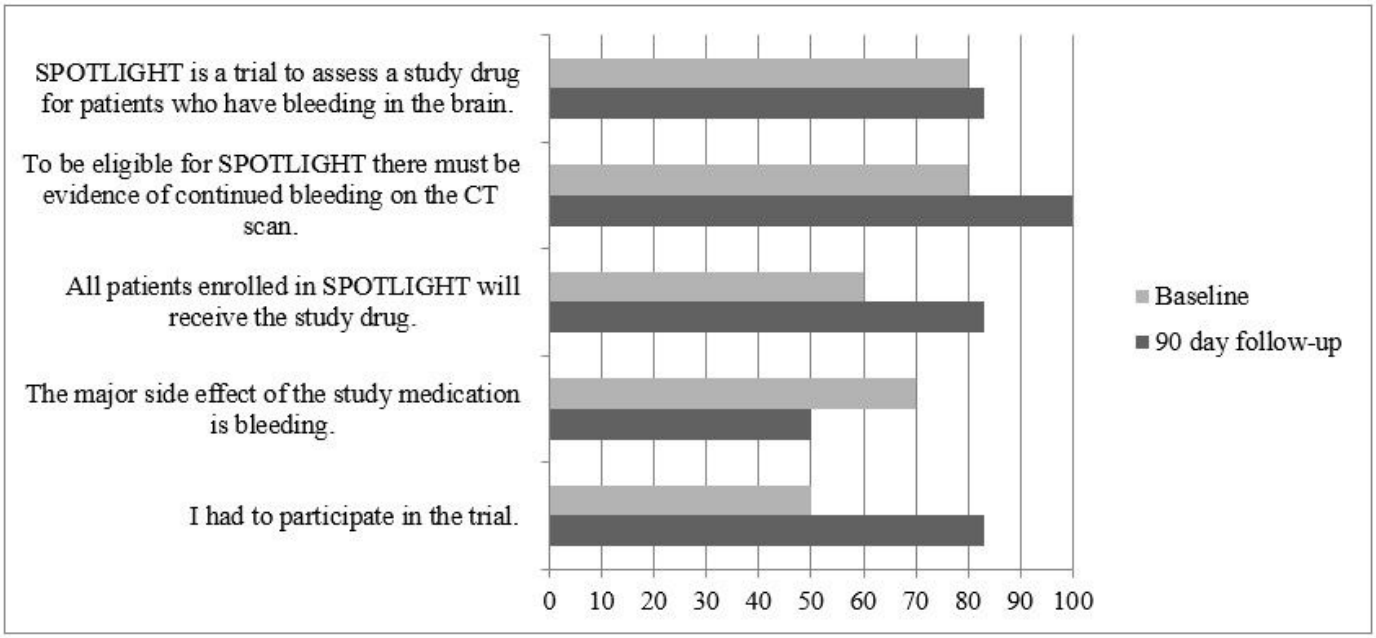

Figure 1

Percentage (%) of participants responding correctly to questions about the SPOTLIGHT trial.