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Study protocol for a multicentre pragmatic nested randomised clinical trial (SIMPLY-SNAP trial)

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Evaluating the impact of a SIMPlified LaYered consent process on recruitment of potential participants to the *Staphylococcus aureus* Network Adaptive Platform trial: study protocol for a multicentre pragmatic nested randomised clinical trial (SIMPLY-SNAP trial)

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ABSTRACT

Introduction Informed consent forms (ICFs) for randomised clinical trials (RCTs) can be onerous and lengthy. The process has the potential to overwhelm patients with information, leading them to miss elements of the study that are critical for an informed decision. Specifically, overly long and complicated ICFs have the potential to increase barriers to trial participation for patients with mild cognitive impairment, those who do not speak English as a first language or among those with lower medical literacy. In turn, this can influence trial recruitment, completion and external validity.

Methods and analysis SIMPLY-SNAP is a pragmatic, multicentre, open-label, two-arm parallel-group superiority RCT, nested within a larger trial, the *Staphylococcus aureus* Network Adaptive Platform (SNAP) trial. We will randomise potentially eligible participants of the SNAP trial 1:1 to a full-length ICF or a SIMPlified LaYered (SIMPLY) consent process where basic information is summarised with embedded hyperlinks to supplemental information and videos. The primary outcome is recruitment into the SNAP trial. Secondary outcomes include patient understanding of the clinical trial, patient and research staff satisfaction with the consent process, and time taken for consent. As an exploratory outcome, we will also compare measures of diversity (eg, gender, ethnicity), according to the consent process randomised to. The planned sample size will be 346 participants.

Ethics and dissemination The study has been approved by the ethics review board (Sunnybrook Health Sciences Research Ethics Board) at sites in

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ The SIMPLY-SNAP trial has a unique Study Within A Trial design that evaluates an innovative consent process within an operating clinical trial setting, which is likely to have greater validity compared with previous work that evaluated consent forms in healthy volunteers or simulated patients.
⇒ If the simplified consent process is found to be superior (a higher proportion of eligible patients given consent) to the full-length consent form, the findings from this study could be transformative to the informed consent process for randomised clinical trials.
⇒ Patient engagement throughout the study design process has ensured selection of patient-relevant secondary outcomes and development of patient-centred consent material and study questionnaires.
⇒ This study lends an equity, diversity and inclusion lens to clinical trial consent by exploring the sociodemographic factors that influence informed consent and clinical trial participation, as well as quantifying population diversity in the patient population enrolled in the SNAP trial via the two different consent approaches.
⇒ Simplified consent may not be suitable for all trial types, for example, new compounds or studies where the risks of therapy are less clearly defined. Findings may be most generalisable to comparative effectiveness trials of therapies currently used in clinical practice.

Ontario. We will disseminate study results via the SNAP trial group and other collaborating clinical trial networks.
Trial registration number ClinicalTrials.gov Registry (NCT06168474; www.clinicaltrials.gov).

INTRODUCTION

Current consent processes for randomised clinical trials (RCTs) can be onerous, with informed consent forms (ICFs) that have the potential to overload patients with too much information at the expense of conveying the salient elements that underpin an informed decision.[1 2] Many patients do not read the entire form, and among those who do, understanding is often compromised.[1–5] A previous systematic review showed that up to half of patients recruited to clinical research studies failed to demonstrate understanding of key basic components such as the risks and benefits of treatment or their ability to withdraw from the study.[5] ICFs may also overemphasise treatment risks due to regulatory obligations requiring an exhaustive list of potential risks, however minor or remote.[6] For comparative effectiveness research involving practices within the current standards of care, these risks may also not exceed those encountered in routine clinical practice.[6]

These issues are clearly illustrated within the context of the *Staphylococcus aureus* Network Adaptive Platform (SNAP) trial (ClinicalTrials.gov identifier: NCT05137119). SNAP is a large pragmatic international multicentre platform trial which aims to answer a range of clinically important questions about the management of *S. aureus* bacteraemia (SAB).[7–9] Patients with SAB can be critically ill during their initial hospitalisation—the window of opportunity for enrolment in such a trial. It is imperative therefore that patients and/or their substitute decision-makers can receive and understand the essential trial elements that constitute an informed decision. This may be especially true when testing interventions which have the potential to reduce morbidity or mortality.

Lengthy, complicated forms may also deter potential participants from enrolling in RCTs, potentially posing challenges to recruitment rates.[10] Poor recruitment is a common reason why RCTs cannot be completed, and difficulties with the informed consent process have been highlighted as a potential contributory factor.[11] Furthermore, this negative impact on recruitment rates may not apply equally to all patients. The writing level and complexity of current consent forms have the potential to create a bias toward the recruitment of more educated and literate patients.[12 13] This can inadvertently deprive underprivileged or marginalised sectors of society from participation in clinical research.[14] Patients of minority ethnic background have been shown to be less likely to be enrolled in research studies.[15 16] Greater diversity can improve generalisability of trial results by making a trial population more representative of the general population. Emphasising this importance, the US Food and Drug Administration has issued guidance that clinical trial sponsors should have plans for increasing enrolment of participants from historically under-represented racial and ethnic populations.[17] Simplified consent is one strategy that may achieve this aim. This problem applies specifically to bloodstream infections as well, where patients are often critically ill or with impaired decision-making capacity. A scoping review by our team identified existing lengthy consent processes as a major barrier to improving external validity and generalisability in bloodstream infection RCTs.[18]

To address these limitations with existing consent processes, as part of the SNAP trial, a SIMPlified LaYered (SIMPLY) consent process was developed, whereby basic information is provided in a more accessible format (shorter in length and in simple point-form language), with embedded links for participants who desire more detailed information. A previous pilot qualitative study in Australia conducted interviews with focus groups of previous survivors of SAB and found that such an approach was strongly supported.[19] A major emergent theme was the added value of agency because the participants were able to prioritise their own information needs and exert a degree of control over the amount of information processed, particularly during a time of illness. This addresses variations in the needs or characteristics of potential participants and may ensure that information is appropriately individually tailored. Based on these findings, this consent process has been adopted at SNAP trial sites in Australia. However, the simplified consent process was not adopted throughout Canada during initial operationalisation of the SNAP trial. While this natural experiment could allow for an observational comparison between Australia and Canada, such a comparison may falsely attribute differences in recruitment to the consent process and not to the many other differences between the Australian and Canadian environments. Therefore, we designed a nested RCT within live Canadian SNAP trial sites which will randomise patients to simplified layered consent or the full-length ICF.

METHODS AND ANALYSIS

Study design

SIMPLY-SNAP will be a pragmatic, multicentre, open-label, two-arm parallel-group superiority RCT, nested within the larger SNAP trial.[7] This nested study design has also been previously referred to in the literature as a Study Within A Trial, designed to evaluate alternative ways of delivering or organising a specific component of a clinical trial.[20] The trial has commenced recruitment on 28 November 2023, and will end when the target sample size is accrued.

Hypotheses

We hypothesise that, for potential SNAP trial participants (or substitute decision-makers), the use of a simplified layered consent process compared with full-length consent process will lead to an increased rate of study

participation (primary hypothesis). Secondary hypotheses include improved participant understanding and satisfaction, and the inclusion of a more diverse trial population.

Setting

SIMPLY-SNAP will be conducted at selected participating SNAP trial sites in Canada. The regional coordinating centres will be the Research Institutes of the McGill University Health Centre and Sunnybrook Health Sciences Centre. The full list of SIMPLY-SNAP study sites is available online at the ClinicalTrials.gov registration (NCT06168474) and will be regularly updated as new sites are included.

Participants

SIMPLY-SNAP participants will be those who are eligible for enrolment in the SNAP trial at participating sites. For patients below the legal age of consent or without decision-making capacity, their surrogate decision-makers will be approached. We will follow local research ethics guidance for any eligible minors in accordance with Canadian guidelines.[21]

Inclusion criteria

- All inclusion criteria from the larger SNAP trial:
  a. *S. aureus* complex grown from more than one blood culture.
  b. Admitted to a participating hospital at the time of eligibility assessment.
- Specific additional inclusion criteria for SIMPLY-SNAP:
  a. Admitted to participating hospital of SIMPLY-SNAP.
  b. Self-reported proficiency in English or French adequate to be able to participate in consent process carried out solely in English or French (as the supplemental consent materials required in the simplified consent process are currently only available in these two languages).

Exclusion criteria

- All exclusion criteria from larger SNAP trial:
  a. Time of anticipated platform entry is greater than 72 hours post-collection of the index blood culture.
  b. Polymicrobial bacteraemia, defined as more than one organism in the index blood cultures, excluding those organisms judged to be contaminants by either the microbiology laboratory or treating clinician.
  c. Patient currently being treated with a systemic antibacterial agent that cannot be ceased.
  d. Known previous participation in SNAP.
  e. Known positive blood culture for *S. aureus* between 72 hours and 180 days prior to the time of eligibility assessment.
  f. Treating team deems enrolment in the study is not in the best interest of the patient.
  g. Treating team believes that death is imminent and inevitable.
  h. Patient is for end-of-life care and antibiotic treatment is considered inappropriate.
  i. Patient less than 18 years of age and paediatric recruitment not approved at recruiting site.
- Specific additional exclusion criteria for SIMPLY-SNAP: none

Trial interventions

For participants randomised to the SIMPLY-SNAP experimental group, a simplified layered consent process will be used to explain information for the SNAP trial. The research staff member obtaining consent will provide a standardised explanation, providing summarised information in simple English or French contained in a four-page concise participant information sheet (see online supplemental appendix). This information sheet will include the essential elements of trial consent, including an explanation of the trial procedures, data and sample collection, and follow-up information.[21] The sheet also outlines important ethical considerations for patients, such as confidentiality, regulatory and safety requirements, the ability to dropout, and the necessary process and contact numbers for grievances or feedback. In addition to the text, the form includes links to additional written information and videos that can be accessed on top of the simplified ICF (ie, the additional layers in the layered consent process). These materials are hosted on the SNAP trial website (https://www.snaptrial.com.au/patients) and are available in both English and French. Participants will be able to access these directly through embedded hyperlinks using provided electronic tablets. Throughout the consent process, the research staff member or site investigator will answer any questions that the participant has as per the Good Clinical Practice informed consent process guidelines.

For participants randomised to the control group, the existing consent process will be used including going through the currently approved full-length ICF, with all information provided upfront. Similarly, throughout the consent process, the research staff member or site investigator will answer any participant questions.

Randomisation and allocation concealment

Randomisation will be conducted through a secure website using a computer-based central randomisation program hosted by the SNAP trial. Allocation will be in a 1:1 ratio with block randomisation and randomly varying block sizes of either 2, 4 or 6 to maintain allocation concealment. We plan to stratify randomisation by centre as we anticipate between-centre differences in recruitment success due to differential patient volumes, patient populations and staff research experience. Similarly, we will stratify by whether consent is given by the participant or a surrogate decision-maker, as we anticipate that recruitment success could vary depending on who is giving the consent. Lastly, we will stratify by consenting language (English or French) as there may be linguistic or cultural differences associated with language.

Protecting against sources of bias

Contamination bias

To mitigate between-arm contamination bias, research staff members at study sites participating in SIMPLY-SNAP will be trained in the two different consent forms and instructed to use standardised explanations depending on which form is being used. However, as this is a pragmatic trial intended to evaluate the implementation of a novel consent process in a live and enrolling clinical trial, real-time audits will not be conducted, nor will the consent process be recorded for retrospective assessment of strategy adherence. As such, there may be a degree of contamination between arms which we accept as a limitation of the trial design and the pragmatic implementation of such a consent intervention; any intervention contamination should bias the results towards the null. Furthermore, the choice of embedding SIMPLY-SNAP within a larger clinical trial is in line with our aim of studying the impact of an intervention in real research practice, in which varying adherence to consent processes is also possible.

Ascertainment bias

SIMPLY-SNAP will be an open-label study because blinding of the two different consent processes is not feasible. Therefore, neither participants nor research staff administering consent will be blinded to intervention allocation. However, to minimise outcome ascertainment bias, analysis of primary and secondary outcome results will be performed by a blinded statistician. The assessor of the secondary outcomes of participant satisfaction and understanding will also be a separate blinded research staff member who was not involved in the consent process.

Withdrawal from study

Study withdrawals will likely be rare, because of the point intervention, immediate assessment of the primary outcome, same-day secondary outcome assessment and no subsequent follow-up. Dropouts post-randomisation but before the consent process for SNAP can be started (eg, if the patient dies or is transferred to another hospital) will be exceedingly rare.

Protocol adherence and protocol deviations

There is no expected protocol non-adherence as the intervention is a point intervention delivered by the research staff. Participants may decline completion of secondary outcome measurement questionnaires, and these will be treated as missing data.

Frequency and duration of follow-up

Screening, randomisation, intervention and primary outcome measurement will all be completed on the same calendar day. Secondary outcome assessment via completion of the post-consent questionnaires will be completed within 3 days after consent. The trial flow diagram is shown in figure 1.

Primary outcome

The primary outcome will be the proportion of patients who consent and are randomised in the SNAP trial, out of all SNAP-eligible patients randomised in SIMPLY-SNAP. This is an objective binary outcome that will be assessed immediately after the consent intervention and corresponds to the percentage of eligible subjects recruited, which is an important metric for clinical trial recruitment success.

Secondary outcomes

The secondary outcomes are critically important to contextualise the primary outcome and include:

a. Participant understanding of the clinical trial (see below).
b. Participant satisfaction with the consent process, as scored by an 11-point Likert scale (0–10, where 0 indicates 'not satisfied at all' and 10 indicates 'extremely satisfied').
c. Research staff satisfaction with the consent process, as scored by an 11-point Likert scale (0–10, same scale as (b)).
d. Time taken for the entire consent process (in minutes) (see below).

Understanding of the clinical trial will be measured by a modified Consent Understanding Evaluation (CUE) tool (see online supplemental appendix). This questionnaire will be administered after the consent process by a separate assessor blinded to the intervention allocation arm. It comprises a list of open and closed-ended questions designed to evaluate a participant's understanding of the clinical trial they just enrolled in, with a maximum possible score of 15. The questionnaire is adapted from previous similar trials evaluating adjunctive consent interventions, but with questions contextualised to assess understanding of specific features of the SNAP trial.[22 23]

We will evaluate satisfaction scores from both participant and research staff perspectives, to compare overall satisfaction between the simplified consent process and the full-length consent processes. A Likert scale was chosen instead of a longer survey to minimise data collection burden and maximise convenience for the participant. Further in-depth opinions about the consent process will be studied in a selected subgroup of participants and research staff who volunteer to participate in a separate qualitative follow-up substudy (ethics approval and funding to be sought separately).

Time taken for the entire consent process will be standardised as: starting from the point of randomisation in SIMPLY-SNAP and ending at point of entering the consent decision into the SNAP database. This will be measured using a stopwatch application on a smartphone. The time in minutes will be rounded up to the next whole minute.

Exploratory outcome measures

As an exploratory outcome, we will also evaluate diversity of the enrolled trial population across five self-reported sociodemographic characteristics: gender,

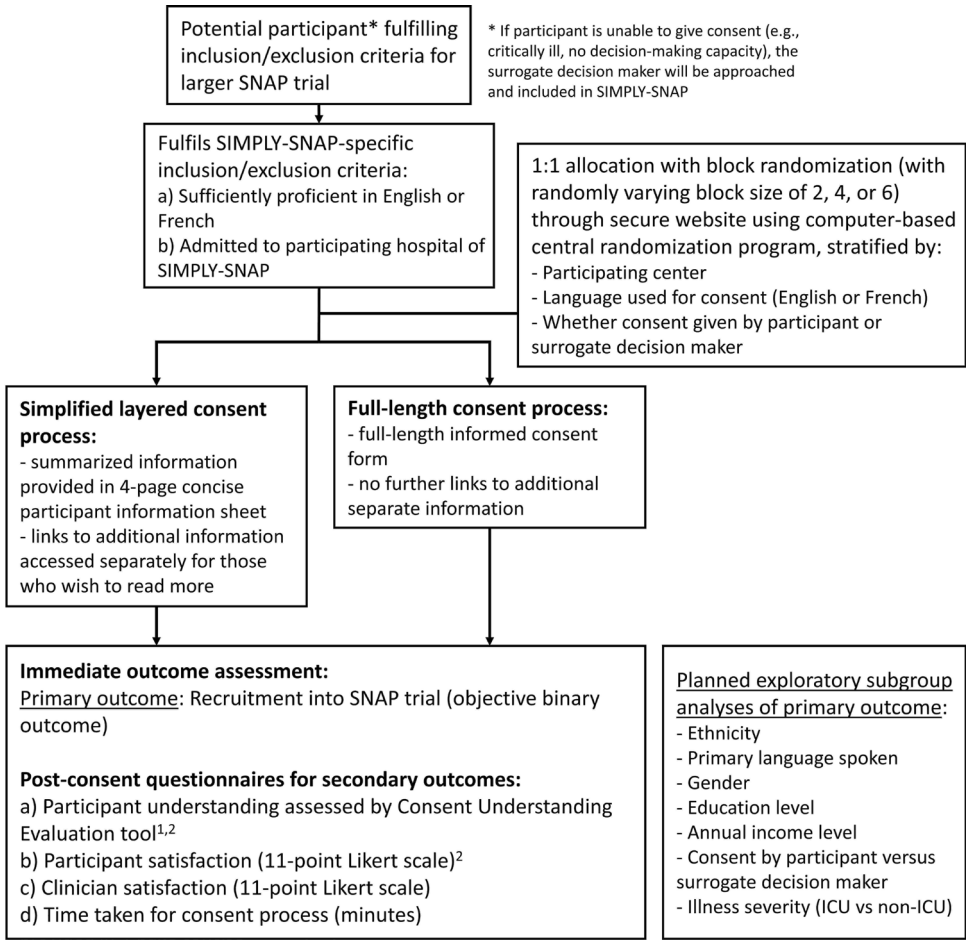

Figure 1 Trial flow diagram. [1]This tool is adapted from existing instruments used in previous consent studies and comprises a variety of open-ended and closed-ended questions to measure participants' understanding of the clinical trial they are enrolled in. [2]Secondary outcomes (a) and (b) will be evaluated by a blinded assessor who was separate from the consent-taking process. ICU, intensive care unit.

ethnicity, primary spoken language, socioeconomic status (measured by income level or last income level before retirement) and highest formal educational level attained. These data will be collected after the consent process and will be based on participant self-reporting. These variables were chosen based on the PROGRESS framework which summarises sociodemographic characteristics that are important determinants of health.[24]

We will separately evaluate diversity of the patient group enrolled in SNAP via the simplified consent process versus the patient group enrolled via the full-length consent form. Diversity will be measured using the Simpson's Diversity Index (SDI), a measure of population diversity that is commonly used in sociology and demography.[25] SDI will be calculated for each of five sociodemographic variables for the group recruited via simplified consent and the group recruited via full-length consent. A composite diversity score for each group combining the SDIs of all five variables will also be calculated using methods previously described.[26 27]

Statistical analysis

Analysis of primary outcome

The estimands framework outlining the various planned analyses is summarised in table 1.[28] The primary outcome will be analysed using a mixed logistic regression model with recruitment to SNAP as the binary outcome variable and intervention arm as the primary exposure variable. Stratification variables of language and consenting person (patient vs surrogate decision-maker) will be included as fixed-effect covariates, while study site will be included as a random effect (ie, with random intercept). The latter accounts for clustering by study site, which is expected given intersite variation in recruitment rates, influenced by site-specific factors such as individual research staff. This model will provide the adjusted OR for the primary outcome. The adjusted risk difference will also be estimated from this model with bootstrapped 95% CIs.[29]

The primary analysis will be with the intention-to-treat (ITT) principle, including all participants randomised in SIMPLY-SNAP. An additional modified ITT analysis will be conducted, excluding participants who were randomised but could not be approached by research staff (eg, in event of death or hospital transfer between the point of randomisation and the point research staff make initial contact with the patient). Lastly, an additional per-protocol analysis will be conducted, including only participants in whom a complete consent discussion

Table 1 Estimand framework for primary and secondary estimands

Estimand/objective*	Endpoint	Population-level summary	Intercurrent events strategy
Estimand 1 (primary estimand): To evaluate the effect of being allocated simplified consent vs full-length consent on the probability of recruitment to the SNAP trial in SNAP-eligible patients randomised to the SIMPLY-SNAP trial	Primary outcome: recruitment to SNAP trial (defined as consent signed and randomised within SNAP)	Absolute risk difference	Treatment policy strategy (intention-to-treat principle)
Estimand 2: To evaluate the effect of completed simplified consent discussion vs full-length consent discussion on the probability of recruitment to the SNAP trial in SNAP-eligible patients	Primary outcome: recruitment to SNAP trial (defined as consent signed and randomised within SNAP)	Absolute risk difference	Principal stratum strategy (only including participants who had a complete consent discussion)
Estimand 3: To evaluate the effect of completed simplified consent discussion vs full-length consent discussion on participant understanding of the SNAP trial	Secondary outcome: participant understanding of the SNAP trial, as measured by 15-point ordinal scale	Adjusted OR	Principal stratum strategy (only including participants who had a complete consent discussion)
Estimand 4: To evaluate the effect of completed simplified consent discussion vs full-length consent discussion on participant satisfaction with the consent process	Secondary outcome: participant satisfaction with the SNAP trial, as measured by 11-point ordinal scale	Adjusted OR	Principal stratum strategy (only including participants who had a complete consent discussion)
Estimand 5: To evaluate the effect of completed simplified consent discussion vs full-length consent discussion on research staff satisfaction of the SNAP trial	Secondary outcome: research staff satisfaction with the SNAP trial, as measured by 11-point ordinal scale	Adjusted OR	Principal stratum strategy (only including participants who had a complete consent discussion)
Estimand 6: To evaluate the effect of being allocated simplified consent vs full-length consent on the time taken for the consent process	Secondary outcome: time taken for the consent process (from time of SIMPLY-SNAP randomisation to time of consent decision)	Adjusted OR	Treatment policy strategy (intention-to-treat principle)
Estimand 7: To evaluate the effect of age, gender, ethnicity, primary spoken language, income level, educational level and illness severity on the probability of recruitment to the SNAP trial in SNAP-eligible patients	Primary outcome: recruitment to SNAP trial (defined as consent signed and randomised within SNAP)	Adjusted OR	Treatment policy strategy (intention-to-treat principle)

Continued

Table 1 Continued

Estimand/objective*	Endpoint	Population-level summary	Intercurrent events strategy
Estimand 8: To evaluate, among patients allocated to simplified consent, the effect of accessing adjunct consent materials (number of supplemental videos viewed and amount of time spent on SNAP website) on the probability of recruitment to the SNAP trial	Primary outcome: recruitment to SNAP trial (defined as consent signed and randomised within SNAP)	Adjusted OR	Principal stratum strategy (only including participants who had a complete consent discussion)

*The population for all estimands is the population defined by eligibility criteria: patients in Canadian secondary or tertiary hospitals participating in SIMPLY-SNAP who are screened eligible for entry into the SNAP trial and randomised to either simplified or full-length consent in SIMPLY-SNAP. The treatment condition for all estimands is the simplified consent process versus the full-length consent process as defined in the main manuscript.

was made (eg, excluding patients with whom research staff made contact, but who declined listening to any explanation of the trial).

Secondary non-inferiority hypothesis

If superiority is not demonstrated for the primary outcome, we will assess for non-inferiority of the simplified consent process. This is because even if simplified consent is not shown to be superior in terms of recruitment proportion, it may still be advantageous with regard to the secondary outcomes, and thus there may still be rationale in adopting this consent approach if recruitment proportions are similar to the full-length form. This approach is supported by guidance from the Food and Drug Administration and European Medicines Agency, both of whom state that switching from a superiority to a non-inferiority question in the same trial is acceptable methodologically, as long as the non-inferiority margin is stated in advance, and that the trial is conducted in accordance with non-inferiority trial principles.[30 31] Based on discussion with members of the SNAP Global Trial Steering Committee, we have selected a non-inferiority margin of −5%, that is, that the lower CI of the absolute recruitment proportion in the simplified consent arm is no more than 5 percentage points lower than the full-length consent arm.

Subgroup analyses

To evaluate the impact of different sociodemographic and clinical characteristics on the relationship between the consent process and recruitment outcome, prespecified exploratory subgroup analyses will be conducted for the primary outcome comparing age (<65 years vs ≥65 years), gender (man, woman, other), ethnicity, primary language spoken (English, French, other), annual (pre-retirement) household income level (<$50 000/year, $50 000–$100 000/year, >$100 000/year), educational level, consenting person (participant vs surrogate decision-maker) and illness severity (in intensive care unit (ICU) vs non-ICU at randomisation). Subgroup analyses will be conducted using a formal test of interaction and effect sizes will be reported using a forest plot. No adjustment for multiple testing will be conducted and findings will be considered exploratory.

Analysis of secondary and exploratory outcomes

Secondary outcomes of patient understanding and patient/researcher satisfaction will be treated as ordinal outcomes and analysed using mixed proportional odds models, adjusted for language and consenting person as fixed-effect covariates and study site as a random effect. If the proportional odds assumption is not satisfied, we will either apply a partial proportional odds model or perform individual logistic regressions for each cut-off point on the ordinal scale, whichever is more appropriate.[32] Time taken for the consent process will be analysed using a linear mixed model, adjusted for the same fixed and random effects. The same mixed-model approach was taken since recruitment at most study sites is conducted by a small number of research staff, which is likely to give rise to clustered measurements, in particular satisfaction scores.

For the exploratory outcome of diversity of the recruited populations, we will only descriptively report the individual SDI for each of the five sociodemographic variables along with the overall composite SDI for the two enrolled groups, without conducting statistical testing for this outcome as this outcome is assessed at the cohort level and there is only one sample per group (one SDI per arm).

Sample size calculation

The sample size calculation was based on both the primary superiority hypothesis and the secondary non-inferiority hypothesis, with the final sample size taken as the larger of the two calculated sample sizes. The first calculation was based on testing the null hypothesis of no difference in proportions of recruitment success (into the larger

SNAP trial) between the two intervention arms. In discussion with the SNAP Global Trial Steering Committee, the minimally clinically important difference in recruitment success rates of 15 percentage points was defined. Using estimates based on the current proportion of eligible SNAP patients consented in Canada, a 70% recruitment rate for the full-length consent form was chosen as the control event rate. With an anticipated 85% recruitment rate for the simplified consent process, an alpha level of 0.05, power of 90% and a two-sided null hypothesis test, the calculated minimum sample size requirement is 161 participants per arm (total 322 participants).

For the secondary non-inferiority hypothesis, we assumed that the simplified layered consent process would be slightly better than the full-length consent form but would not meet the criteria for superiority. Assuming an 80% success rate in the intervention group vs 70% in the control group, with a non-inferiority margin of −5% (ie, excludes a difference in favour of the full-length consent process arm of more than 5 percentage points), we calculated the number of patients required at 173 participants per arm (total 346 participants; 90% power, 2.5% one-sided alpha).

We took the larger of the two calculation results (346 patients) as the final sample size. We did not inflate sample size for a potential dropout rate since primary outcome assessment occurs immediately post-randomisation and intervention.

Loss to follow-up and missing data

No missing data are expected for the primary outcome since recruitment success is evaluated immediately post-consent for all patients. However, as secondary outcomes of participant satisfaction and understanding are assessed through completion of questionnaires post-consent, there may be some missing data if participants decline completion of these questionnaires. All attempts will be made to minimise the proportion of missing data, and the primary analysis for secondary outcomes will be a complete case analysis excluding participants with missing data. In the event missing data proportion is greater than 10%, we will conduct two additional sensitivity analyses: (1) imputing the missing secondary outcome with the median score of that treatment group, and (2) best case/worse case analyses imputing the missing secondary outcome with the best score/worst score of that treatment group. Statistical analyses will be conducted by a blinded statistician.

Exploratory analyses

To separately evaluate independent predictors of trial recruitment, we will additionally include in the primary mixed-effect model covariates of age, gender, ethnicity, primary spoken language, income level, educational level and illness severity.

Lastly, we will also measure in the intervention group (simplified consent) whether participants or surrogate decision-makers accessed the SNAP website, viewed the supplemental videos and the amount of time spent on reading the supplemental information, by asking participants to report these usage indicators. These will be reported descriptively, but we will also assess if these are associated with recruitment success by adding these additional variables to the same mixed-effect model, for the subset of patients randomised to simplified consent only.

Frequency of analyses

No interim analysis will be conducted as there are no expected harms or safety concerns with the intervention arms in SIMPLY-SNAP. There will be no interim stopping rules and the consent trial will continue until the target sample size is achieved.

Steering Committee and Data Monitoring Committee

The SIMPLY-SNAP Steering Committee will include all principal investigators, a biostatistician co-investigator and a patient co-investigator with lived experience of *S. aureus* bloodstream infection. The larger SNAP Study has a well-established Data Safety and Monitoring Committee (DSMC), but there will be no DSMC for SIMPLY-SNAP given the minimal risk expected with the study interventions.

Patient and public involvement

The simplified consent process and material were developed through collaboration with three consumer representatives: one with experience in developing educational material, one with previous healthcare experience and a prior SAB survivor.[19] Patient engagement has also been sought throughout the design of this study by closely working with a patient representative on the SNAP Global Trial Steering Committee. These are survivors of *S. aureus* bloodstream infection and participants of previous *S. aureus* clinical trials with their individual lived experiences and are thus able to provide unique viewpoints from a patient perspective. They have provided input on the simplified consent process, the CUE questionnaire and the overall study design.

ETHICS AND DISSEMINATION

Ethics approval

The study has been approved by the ethics review board (Sunnybrook Health Sciences Research Ethics Board) at sites in Ontario. Ethics approvals are underway at participating sites in other provinces in Canada.

Waiver of consent

An informed consent waiver was approved for purposes of SIMPLY-SNAP. This is essential for conduct of SIMPLY-SNAP for two reasons. First, it would be impractical (and illogical) to require a long form consent procedure before enrolling a participant to a study designed to evaluate consent process. Second, and more importantly, such a requirement would compromise the external validity of this trial, since potential participants who decline participation for the consent trial are more likely to decline participation in the larger clinical trial. We would thus

not be able to test the hypothesis that the simplified consent process improves trial recruitment success when applied to an entire cohort of potential trial participants. Participants will be debriefed after the consent process and informed that they were included in a trial testing two different consent modalities.

Expected adverse events

There are no potential expected harms with the intervention or control arms in SIMPLY-SNAP, and hence no adverse event reporting mechanism is in place. However, if participants have grievances or feedback about the consent process, there will be a contact number for them to direct these.

Knowledge dissemination

Study results will be disseminated through multiple venues. Publication in a general medical journal with a broad readership is anticipated given the broad appeal of this subject to a wide variety of research and clinician specialties. This publication will be made open access but no other publication restrictions exist. We will also use these study results to engage with patient advocates and patient representatives working within the SNAP trial network to improve ongoing consent processes.

TRIAL STATUS

This trial commenced recruitment in November 2023.

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