TITLE

A WebApp for Sample Size calculation and evaluation of PROGRESSion criteria in pilot and feasibility studies (SS-PROGRESS)

ABSTRACT

We have developed an easy-to-use and freely available web app for researchers that will help in the design and evaluation of pilot and feasibility studies based on the methodology of Lewis et al.[1] At the design stage the web app is used to determine the sample size needed for the pilot study based on a set of pre-specified progression criteria using a hypothesis-testing approach. At the end of the pilot study the web app is used as an aid to decide whether a main trial is feasible based on a traffic light (RED, AMBER, GREEN) evaluation of the progression criteria.

The web app, written in R-Shiny[2] has been developed by the research team and tested and reviewed by external experts from other national CTUs. It includes a set of tabs giving a brief description of the methodology with examples, a sample size calculator with clear instructions and an evaluation screen, as well as relevant contact details and references, providing researchers with an accessible platform on which to derive required sample sizes to meet their feasibility objectives and to evaluate their data. The web app will facilitate improved design and evaluation of future pilot and feasibility studies, leading to studies that properly inform various stakeholders regarding progression to main trials.

INTRODUCTION

Lewis et al.[1] recently outlined a principled and robust method of sample size determination for pilot and feasibility studies that is based on hypothesis tests of multiple feasibility outcomes that may comprise progression criteria. Their approach aimed to provide researchers with a methodology for determination and evaluation of pilot and feasibility studies (PAFS) in the context of the CONSORT recommended reporting guidelines for such studies[3] by focusing on feasibility outcomes (the primary outcome measures for PAFS): such as recruitment, treatment fidelity/adherence and/or follow up. The purpose of this work is to aid decision-making on whether to proceed or not (with or without amendment) to a main trial, which is a key function of a pilot study. Lewis et al.'s approach derives sample sizes for pre-specified progression criteria and links these to the analysis of binary (yes/no) feasibility outcomes against suitably chosen progression cut-offs using a hypothesis testing approach. Whilst the use of hypothesis testing is not recommended for assessing clinical outcomes in underpowered PFS,[3] the authors justify their approach as being appropriate for assessing feasibility outcomes. It gives a standardised framework for sample size derivation, addressing past limitations around sample size not being specifically focused on supporting the evaluation of progression criteria in PAFS.[4] By doing so, it facilitates improved design, monitoring

and evaluation of future PAFS, leading to better studies that properly inform various stakeholders regarding progression to main trials.

Working on the principle that there is likely to be more than one progression criterion involved in appraisal of a pilot study, Lewis et al's approach adopts a multi-criterion perspective on pilot and feasibility progression using a 'traffic-light' approach to evaluation. Sample size estimates are generated for a number of feasibility outcomes (e.g., accrual, dropout, etc.) and the largest of the sample sizes is considered to be that required by the study. The results of the pilot are interpreted in line with the success or failure of these feasibility outcomes. Rather than offering a binary judgment on each hypothesis test, the methodology employs a 'stop (RED) – amend (AMBER) – go (GREEN)' signalling approach, which embraces the potential inconclusiveness in hypothesis tests on small sample sizes, where evidence to stop versus go to full trial is often not overwhelming. The concept is to set up hypothesis testing around progression criteria that tests against being in the RED zone (designating unacceptable feasibility—'STOP') based on an alternative of being in the GREEN zone (designating acceptable feasibility—'GO'). Each test is a 1-sample 1-tailed test including feasibility progression cut-points as test parameters.

In general terms, currently a working statistician who is required to calculate a sample size of any kind by applying a specific methodology has several options: i) take the appropriate academic paper that describes the method and programme the methodology from scratch, or ii) use an off-the-shelf package or web app (which in this case does not exist) to automate much of the work. Calculating/programming from scratch can be time consuming and raise the possibility of human error, so it is usually more efficient and practical to use an off-the-shelf package. Since no digital tool was available for executing the Lewis et al. methodology for sample size derivation and statistical evaluation of feasibility findings against progression criteria we sought funding to create and develop such a tool that would translate our statistical approach to a workable and practical tool for users.

The aim of this project, therefore, was to develop an easy-to-use and freely-available web app for researchers that uses the methodological approach of Lewis et al.[1] and provides this within a tool that can be readily accessed to support in the quick and efficient design and evaluation of PAFS.

METHODOLOGY

To support the statistical methodology of Lewis et al.[1] we have developed a web app written in R-Shiny (a software package that allows users to build an interactive web application using the widely used and free-to-access R statistical programming language).[2] The *SS-PROGRESS web app* allows statisticians and trialists to quickly and efficiently implement the methodology and receive their sample sizes, and subsequently evaluate their hypothesis-testing results, extracting graphics that can easily be inserted into reports. It includes tabs for providing: an introduction and description of the methodology as detailed in Lewis et al.,[1] a platform for researchers to enter their progression criteria including cut-offs and test parameters for deriving

sample size, and a means by which researchers can enter accruing and final data and extract a summary report that evaluates summary data against pre-specified progression cut-offs. The web app is hosted on a secure Amazon Web Service server and no data from front-end users will be stored or be accessible by the web app design and maintenance team. It is free to access via a browser on a variety of platforms, including Windows, Mac OS and iOS, Linux, and Android. Only the website address is required for access, the link is: https://ss-progress.shinyapps.io/ss_progress_app/

We extracted a list of key feasibility objectives from a review of select published manuscripts.[3,5-7] The most common feasibility outcomes for which progression criteria were specified were recruitment, retention, and treatment fidelity/adherence. To keep the methodology consistent with our findings we focused on binary feasibility measures around e.g., percentage recruitment, percentage of participants retained and percentage fidelity/adherence of participants with treatment protocol (overall or by treatment group). We aligned the extracted feasibility objectives from the review to three hierarchical levels (population level, participant level, treatment group level), which form the basis of our 2-step sample size derivation. The feasibility outcomes could then be evaluated against the a priori progression cut-offs, with formal decision making justifiable in the context of a sufficiently large and adequately powered pilot study.

A beta version of the web app was tested by two statisticians at Manchester CTU (Ryder and Sylvestre – see Acknowledgements). A list of snags was identified and relayed to the research team, who made the required changes. An advanced version of the SS-PROGRESS web app was later reviewed and discussed in a half-day virtual meeting with an expert panel made up of three independent senior peers with an interest and expertise in pilot sample size methodology from other UK CTUs (Julious, Teare, Wilson – see Acknowledgements). The research team then refined and finalised the web app based on the constructive feedback received.

RESULTS and CONCLUSION

Upon navigating to the web address of the SS-PROGRESS web app, the user is presented with a home screen and a series of tabs, detailed below:

‘Welcome Page’: Within this tab there are five sub tabs; (i) About – which details the background to the study and purpose of the web app; (ii) Feasibility objectives – which details the 3 levels of feasibility measures and provides examples of feasibility objectives at the different levels; (iii) Methodology – which describes the underlying statistical methodology; (iv) Tiering – which explains two ways of evaluating the pilot data, and (v) Sample size extrapolation – which details the 2-step process in deriving the overall sample size for the study.

‘Instructions’: Within this tab, the ‘Text’ sub-tab presents detailed technical instructions on how to use the web app, which will also be available to download as a PDF to allow users to use the app and read the instructions concurrently. Four short (5–10-minute) tutorial videos are available within the ‘Videos’ sub tab

and give an audio-visual presentation by members of the research team on: 1) “Background”, 2) “Methodology”, 3) “Sample size calculator”, and 4) “Evaluation”. The ‘Reporting Template’ sub-tab includes a suggested text template to summarise the output from the evaluation post sample size extraction.

‘Sample size calculator’: This tab gives the individual and overall sample sizes for given sets of feasibility outcomes and allows specification of the test parameters (alpha, beta) and statistical distribution (Normal with continuity correction or Binomial exact) by the users. Users will input details on their feasibility objectives and progression cut-off values directly within text boxes on the webpage. Individual sample size requirements for each test will be shown along with adjusted sample sizes that take into account the sample size requirements across all objectives and the conditional power for each test. A summary of overall sample size recommendations across all feasibility levels is provided at the bottom of the webpage. Users are able to easily change, either up or down, their progression cut-off values and/or change test parameters and assess the impact of these changes on the sample size recommendations.

‘Evaluation’: This tab allows users to input their own (numerator and denominator) data – as observed at that time-point during or at the end of the trial – and assess the current data against the pre-set progression criteria/cut-offs. Current proportion (ratio of numerator to denominator) is automatically generated and this, alongside the pre-specified progression cut-offs, are displayed within a graph to the right of the screen. This feature can be used both on a continual basis for study monitoring and as a final check to inform decision making before moving on from the pilot stage. Additionally, users will be able to edit and export publication-quality plots displaying the results of the hypothesis tests for use in reports and publications.

‘Examples’: This tab includes an illustration of the results and recommendations provided by SS-PROGRESS for four worked examples (including a main example (as detailed in the Lewis et al.[1] paper) and three further examples). For each example, we provide detail and showcase the SS-PROGRESS outputs within separate tabs for: ‘Synopsis’, ‘Sample size calculator’, ‘Evaluation’ and ‘Example report’.

‘Contact Information’: This tab provides contact information for the research team who have developed SS-PROGRESS.

‘FAQs, Events, Publications’: This tab highlights key and frequently asked questions and highlights past and future events/workshops as well as important publications of the SS-PROGRESS work.

‘References’: The final tab provides key publications related to and included within SS-PROGRESS.

The SS-PROGRESS web app is designed to aid standardisation of data collection and reporting of pilot/feasibility trials across the whole field (through application of the underlying Lewis et al.[1] methodology). Its uptake will lead to more robust

conclusions from such studies. The key audiences for the resources from this project are: a) statisticians and methodologists; b) clinical researchers; c) study and data managers; d) funders; e) journal editors/reviewers; and f) study oversight committees.

The web app provides a simple and accessible platform for the methodology of Lewis et al.[1] on formal sample size derivation and evaluation of PAFS, focused on testing against defined progression criteria cut-offs. The outputs will address the current challenges around sample size and progression in PAFS through use of the web app and its wider publication and demonstration. This will facilitate the design, monitoring and evaluation of future PAFS, leading to better studies that can properly inform progression to main trials.

DISSEMINATION

The SS-PROGRESS web app: The primary output from this project is the web app. The web app will facilitate the standardisation of data collection and reporting of PAFS across the whole field. The web app is freely and openly available/accessible.

Peer-reviewed journal article(s): The affiliated methodology paper has been published (Lewis et al.).[1] Detail on the development and features of the SS-PROGRESS web app is being written up for publication in a relevant peer-reviewed journal.

Conference presentations: The development work has been presented at the NIHR Statistics Group conference in Sheffield (2022)[7] and at the International Clinical Trials Methodology Conference (ICTMC) in Harrogate 2022.[8,9] We are targeting further dissemination via future national/international conferences.

Web app workshops: Virtual and/or on-site workshops will be run to demonstrate and assist in the practical use of the web app (targeted forums could include UKCRC registered CTU network, NIHR Statistics Group, MRC Trials Methodology Hub, social media and ALLSTAT e-mailing list).

Contribution of authors: The project was co-led by Lewis (Reader in Medical Statistics, Keele CTU), who was the main author on the associated research article upon which this SS-PROGRESS web app is based, and an experienced research methodologist in the development and implementation of R software, McCray (Research Associate, Keele CTU). The main work on the development of the web app was carried out by Bromley (Research Associate, Keele CTU). Steer and oversight on the development work was provided by Lancaster (Professor of Medical Statistics, Keele CTU), Sim (Professor of Healthcare Research, Keele CTU) and Sutton (Senior Lecturer and Director of Methodology, Manchester CTU). Sutton also led two study statisticians affiliated to Manchester CTU in beta-testing of the web app. Both Lewis and Sutton conceived the original idea.

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