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Corresponding Author:	Timothy James Kendall, B.M., Ph.D. University of Edinburgh Edinburgh, UNITED KINGDOM
First Author:	Timothy James Kendall, B.M., Ph.D.
Order of Authors:	Timothy James Kendall, B.M., Ph.D. Max Robinson Daniel Brierley Shujing Jane Lim Daniel O'Connor Abeer Shaaban Ian Lewis An-Wen Chan David Harrison
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Abstract:	<p>The SPIRIT 2013 Statement provides evidence-based recommendations for the minimum content of clinical trial protocols. Assessment of biospecimens is often required for trial eligibility or as part of outcome evaluation, and precision molecular approaches are increasingly used in trial design. However, cellular and molecular pathology practices within trials have neither been codified nor formalised. We developed international consensus reporting guidelines for cellular and molecular pathology content in clinical trial protocols (the SPIRIT-Path Extension) using an international Delphi process assessing candidate items generated from a prior systematic review, followed by an expert consensus meeting. 74 individuals from five continents responded, including clinicians, statisticians, laboratory scientists, patient advocates, funders, industry representatives, journal editors, and regulators. The SPIRIT-Path guidelines recommend 14 additional items, 7 extensions to the SPIRIT checklist and 7 elaborations, that should be addressed in trial protocols with pathology content alongside the SPIRIT 2013 Statement items. SPIRIT-Path recommends that protocols should document the individuals, processes, and standards for all cellular and molecular pathology components of the trial protocol, including all stages of the specimen pathway, any digital pathology methods, and with specific consideration of the value of trial data and tissue for additional translational studies.</p>

Guidelines for cellular and molecular pathology content in clinical trial protocols: the SPIRIT-Path extension

Timothy J. Kendall, MD* ; Max Robinson, BDS* ; Daniel J. Brierley, BDS; Shujing Jane Lim, MD; Daniel J. O'Connor, MD; Professor Abeer M. Shaaban, MD; Ian Lewis, PhD; Professor An-Wen Chan, MD; Professor David J. Harrison, MD; for the SPIRIT-Path Group.

Author Affiliations: University of Edinburgh Centre for Inflammation Research, University of Edinburgh, Edinburgh, United Kingdom (Kendall); Department of Cellular Pathology, Newcastle upon Tyne Hospitals NHS Foundation Trust, Newcastle, United Kingdom (Robinson, Lim); Unit of Oral and Maxillofacial Pathology, University of Sheffield, Sheffield, United Kingdom (Brierley); The Medicines and Healthcare products Regulatory Agency, London, United Kingdom (O'Connor); Queen Elizabeth Hospital Birmingham and University of Birmingham, Birmingham, United Kingdom (Shaaban); National Cancer Research Institute, London, United Kingdom (Lewis); Women's College Research Institute, Department of Medicine, University of Toronto, Toronto, Ontario, Canada (Chan); University of St Andrews, St Andrews, United Kingdom (Harrison)

*These authors contributed equally.

Corresponding author: Timothy J. Kendall, University of Edinburgh Centre for Inflammation Research, Queen's Medical Research Institute, 47 Little France Crescent, Edinburgh EH16 4TJ, United Kingdom (Tim.Kendall@ed.ac.uk).

Summary

The SPIRIT 2013 Statement provides evidence-based recommendations for the minimum content of clinical trial protocols. Assessment of biospecimens is often required for trial eligibility or as part of outcome evaluation, and precision molecular approaches are increasingly used in trial design. However, cellular and molecular pathology practices within trials have neither been codified nor formalised. We developed international consensus reporting guidelines for cellular and molecular pathology content in clinical trial protocols (the SPIRIT-Path Extension) using an international Delphi process assessing candidate items generated from a prior systematic review, followed by an expert consensus meeting. 74 individuals from five continents responded, including clinicians, statisticians, laboratory scientists, patient advocates, funders, industry representatives, journal editors, and regulators. The SPIRIT-Path guidelines recommend 14 additional items, 7 extensions to the SPIRIT checklist and 7 elaborations, that should be addressed in trial protocols with pathology content alongside the SPIRIT 2013 Statement items. SPIRIT-Path recommends that protocols should document the individuals, processes, and standards for all cellular and molecular pathology components of the trial protocol, including all stages of the specimen pathway, any digital pathology methods, and with specific consideration of the value of trial data and tissue for additional translational studies.

Introduction

The clinical trial protocol is an essential document that describes the rationale and conduct of the proposed research. The document must contain sufficient information to allow review when seeking funding, support the safe and optimal conduct of the study against the trial objectives, and allow subsequent results to be evaluated and compared with other trials^{1,2}. Despite the importance of trial protocols, their quality and content are known to be variable. The SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) 2013 Statement provides evidence-based recommendations for the minimum content of clinical trial protocols to address this variability^{3,4}.

The statement is widely endorsed by medicines developers, academia, regulators and medical journals.

Extensions to the SPIRIT 2013 Statement have been produced to address specific trial protocol elements that are not addressed fully by application of the original guidelines; to date, these relate to patient-reported outcomes⁵, n-of-one trials⁶, and trials evaluating artificial intelligence interventions⁷. A SPIRIT extension item is an additional checklist item that addresses an aspect of protocol content that is not adequately covered by the SPIRIT 2013 Statement, as judged by available evidence and subject-matter expert opinion; a SPIRIT elaboration item is an elaboration of an existing SPIRIT item as it applies to a particular subject area⁵.

Pathological assessment including confirmation of diagnosis is required for determining eligibility or outcome assessment in therapeutic trials of specific conditions, particularly in oncology but also in therapeutic trials in non-neoplastic diseases, for example those with an inflammatory or immune-mediated aetiology or with fibrotic sequelae, and is still regarded as the gold standard⁸. Such clinical trials increasingly use precision molecular approaches in their design, but these do not always capitalise on the richness of data available from full pathological assessment. Despite such technological advances, the crucial decision to determine participant eligibility often relies on traditional subjective assessment of tissue sections by a pathologist. Such practice has neither been codified nor formalised and does not yet fully integrate novel molecular analyses.

SPIRIT-Path is a fully international project coordinated by the UK National Cancer Research Institute's Cellular and Molecular Pathology Initiative (NCRI CMPath) and supported by the SPIRIT group to extend the SPIRIT 2013 Statement, where needed, for trials that include cellular and molecular pathology protocol content. Here we describe the SPIRIT-Path guideline development and provide a checklist with explanations. The extension offers guidance to authors of clinical trial protocols that include pathology activities to ensure all possible steps, including aspects of specimen handling and reporting, are identified at trial inception. Investigators should consider documenting

the pathology methods in a dedicated section of the trial protocol. This will allow trial protocols to comprehensively address cellular and molecular pathology aspects, ensuring adequate skills and resources are available at trial commencement to facilitate the smooth running of laboratory-based components of the trial and fully leverage the value of biospecimens for translational research.

Methods

The SPIRIT-Path project was conceived by members of NCRI CMPath Clinical Trials workstream in May 2019. The SPIRIT-Path Core Group (TJK, MR, SJL, DJB, DOC, AMS, IL, DJH) responsible for the project was established in June 2019 and the SPIRIT-Path International Advisory Group (AWC and all other SPIRIT-Path Ggroup members, appendix pp 25) was assembled shortly afterwards, with the support of the SPIRIT group, to include expert representation from multiple territories and all stakeholder groups in the clinical trials community. A prior systematic review of published guidance was used to identify candidate items was undertaken from January to April 2020⁹. The SPIRIT-Path extension was registered as reporting guidelines under development with the EQUATOR Network in May 2020 and was developed in accordance with the EQUATOR Network's methodology.

Ethical considerations

The project was undertaken by following the UK Research Integrity Office's (UKRIO) Code of Practice for Research and the Universities UK (UUK) Concordat to Support Research Integrity adopted as the University of Edinburgh's Research Integrity framework and was assessed before study commencement using the UKRIO checklist for good practice in research in advance as a peer opinion study. Information was given to Delphi participants in the introductory page of the survey, and electronic informed consent, including for disclosure of participant name and affiliation at publication, was obtained following General Data Protection Regulation best practices and before survey completion (appendix pp 1). Information was given to consensus meeting participants in advance, and consent for the recording of the meeting was obtained at the start of the meeting and before beginning recording.

Candidate item generation

A systematic review to identify and synthesise existing recommendations specific to pathology practice in clinical trials for implementation in trial protocol design published between 1st January 1996 and 13th January 2020 has previously been undertaken⁹. In the prior review, resources were eligible for inclusion if they contained - (1) guidance (in the form of guidelines or expert recommendations) and/or a checklist, which are (2) pathology-related, with (3) content relevant to clinical trial protocols or that could influence a clinical trial protocol design from a pathology perspective. There were no restrictions by language or publication type. The full search strategies for all database and web searches are available in the pre-registered protocol¹⁰. The Core Group and International Advisory Group members and UK Clinical Trials Unit leads were consulted during the review process to identify any additional sources of guidance.

Verbatim extracted guidance was mapped to the SPIRIT 2013 Statement and a provisional list of candidate items was generated by the Core Group. The final list of 48 candidate items was produced after consultation with the International Advisory Group members allowing item revision or addition (appendix pp 3-12).

International Delphi Exercise

Participants

The Core Group members selected participants after consultation with the International Advisory Group members to create an “expert” panel in multiple territories across all stakeholder roles in the clinical trials community. In line with recommendations regarding how to select “experts”¹¹, it was felt those selected were most knowledgeable in this area, representative of the area of inquiry and had considerable practical experience to warrant them “experts”. Participants were also selected to provide international representation from many territories. As those responsible for developing the candidate items, the Core Group members did not provide responses in the Delphi process to minimise potential bias. Characteristics of the 74 Delphi panelists (appendix pp 1-2) were recorded

during the process and are summarised in appendix pp 13-14. Participants included clinicians, clinical trialists, statisticians, trials methodologists, trials and data managers, clinical laboratory scientists, patient advocates, funders, industry representatives, journal editors, and regulators from Africa, Asia, Australasia, Europe and North America.

Rating

Participants were asked to rate the importance of items on a nine-point Likert-type item scale, where '9' represented 'critical' and '1' represented 'not important'. Participants were able to use free-text boxes to justify their scores or offer other items that were not included as candidates.

An item was defined as 'consensus-in' when >70% of participants scored the item as '7-9 (critical)' with <15% scoring '1-3 (not important)'. An item was classified as 'consensus-out' when >70% of participants scored an item '1-3' and <15% of participants scored it '7-9'. All other combinations were considered to be 'no consensus', in accordance with previous research that used similar nine- or ten-point scales¹².

Procedure

A minimum of two rounds was chosen to allow participants to reflect and change their scores between rounds. A third round was not required because of the level of agreement reached by the end of the second round.

Three members of the SPIRIT-Path Core Group (TJK, MR, DJB) piloted the first round and suggested slight amendments to the instructions and wording of some items to ensure they aligned with scoring on a rating scale.

All communication between the researchers and Delphi participants used private, individual email addresses so participants remained anonymous to one another. The Delphi was conducted via Checkbox (Checkbox Survey Inc, Watertown, MA, USA) with links to the Delphi provided in the preparatory emails. For Round One (17th June 2020), participants were given instructions, a consent

form, and the items to rate. Participants were asked to complete the survey by 15th July 2020 and reminder emails were sent to non-responders.

Round Two (10th August 2020) of the Delphi was sent only to those participants who responded to Round One. Participants were advised which items did not reach consensus in Round One and which had been amended based on feedback and asked to re-rate these items.. Participants were also given information from the previous round including their score for each item and the median panel score based on all participants' scores. They were informed that their scores from Round One would be carried forward for any item for which a new score was not returned and asked to complete the survey by 7th September 2020. Reminder emails were sent to non-responders.

Analysis

In Rounds One and Two, response rate, median score and item consensus scores were calculated.

Data were analysed in Excel. In addition, free text comments were reviewed by the SPIRIT-Path Core Group to determine if items needed amendment or additional items required inclusion.

Rationalisation and checklist summary consensus meeting

After the final round of the Delphi exercise, 'consensus-in' items were re-mapped to the SPIRIT 2013 Statement and grouped by theme. For each item, an assessment of the need for an extension or elaboration to the SPIRIT 2013 Statement was made by the Core Group. Items within a theme were combined and draft wording for the extension or elaboration checklist item and explanatory text for each thematic grouping were produced.

The draft document was remotely assessed by the International Advisory Group through two circulations in October 2020, with revisions made after each circulation. After revisions following the second circulation, the candidate SPIRIT-Path items were circulated in advance of a virtual consensus meeting on 4th November 2020, to which all Core Group and International Advisory Group members were invited. The meeting was recorded with the informed consent of participants to allow those unable to attend to contribute. There was an opportunity to discuss items that did not reach

consensus and, for each 'consensus-in' item, the need for either an extension or elaboration was considered. The proposed thematic groupings of each item were discussed in addition to the wording of both the checklist item and the explanatory text.

Following the meeting a final draft of the checklist items and explanatory text was produced by the Core Group. This was circulated for a final time around the International Advisory Group and all members agreed with the wording.

Results

196 invitations to participate in Round One of the Delphi exercise were sent (156 individuals and 40 organisations). 74 individuals consented to participate with 66 fully completing Round One of the Delphi in full; 42 of 48 items reached 'consensus-in' (appendix pp 3-12) while the remainder (items #6, #7, #8, #19, #37 and #42) did not reach consensus. After modification of items without consensus, invitations for Round Two were sent only to those participants who responded in Round One. 46 participants decided to amend their scores from Round One with 44 participants completing Round Two in full; those who did not respond had their Round One scores carried forward into Round Two. Four of the six remaining modified items reached 'consensus-in' (appendix pp 3-12); no consensus was reached for two items (#7 and #42).

SPIRIT-Path Checklist Items and Explanation

The post-Delphi rationalisation process and consensus meeting merged the 46 agreed items by theme, mapped to the SPIRIT 2013 statement (Figure 1 and appendix pp 15-24). The SPIRIT-Path extension recommends that an additional 14 items (seven extensions and seven elaborations, Table 1) that should be addressed in trial protocols with pathology content alongside the SPIRIT 2013 Statement items and other SPIRIT extensions where relevant. These items were considered to be of sufficient significance to trials with any cellular and molecular pathology content that they should be

explicitly addressed in trial protocols. All members of the International Advisory Group agreed with the inclusion of these extension items in this form.

Some items will only apply to clinical trials where there is a requirement for trial-specific specimen activity outside of the routine diagnostic pathway, including the acquisition of trial-specific samples or review/analysis of historical samples; these items are indicated by an asterisk (*).

Administrative information

SPIRIT-Path 5a Elaboration: Specify the individual(s) responsible for pathology content of the trial protocol.

Explanation

The individuals responsible for developing protocol content should be specified. This includes those responsible for protocol content regarding pathology reporting methodology, pathology-specific quality assurance, biospecimen institutional release, movement across trial sites, and archiving and biobanking, where applicable. The documentation of the contributions of specific authors to the trial protocol with affiliations increases transparency, helps identify potential conflicts of interest, and formally recognises the contribution of the pathologists and laboratory scientists to trial development. For protocols describing trial-specific pathology reporting, it is helpful to document the pathologists and translational scientists who have designed or verified the tissue pathway from sample acquisition to analysis to ensure that the 'turn-around times' for scoring and reporting trial data are feasible. Specific documentation of the author responsible for the biospecimen pathway and reporting provides accountability and evidence of consultation with appropriate professionals in protocol design^{13,14}. If there is no involvement of protocol authors with pathology expertise, then a reason should be provided.

SPIRIT-Path 5d Elaboration: Specify how pathology activities and roles are organised in the trial.

Explanation

The organisation of all items related to pathology within the trial should be specified, detailing the responsibilities of the stakeholders. The composition/operation of the Pathology Steering Group or Molecular Tumour Board, if deemed relevant, should be documented, and how representation from these groups and their operation is integrated within the Trial Management Group should be clearly explained. When pathology-based biomarkers are critical to patient recruitment and/or if pathology complete response is the primary outcome measure, a pathologist and/or translational scientist may be included in the Data Monitoring Committee and their role within this committee should be documented. It should be confirmed in the protocol that contractual agreements will be in place between the trial sponsor and the participating centre laboratories concerning the exchange of samples. This information ensures that the required cellular and molecular pathology expertise and responsibilities are clearly defined at trial inception, where applicable, and outlines how trial-specific pathology activity is integrated into overall trial management to maximise the contribution to trial operation^{13,15,16}. It allows readers to understand and evaluate the relevant expertise of those responsible for the pathology aspects of the trial.

Introduction

SPIRIT-Path 6a Elaboration: Describe the pathogenesis of the disease and rationale for any pathology-specific inclusion criteria or endpoints.

Explanation

The cellular and molecular basis of the disease should be described, with justification of the rationale for incorporating any trial-specific biomarkers and any pathology-specific criteria for recruitment. The analytical performance of any laboratory assays (proprietary or laboratory-developed tests) should be described; where these are not known (e.g. if the development of an assay is part of the study), then an evidence-based prediction of performance should be described.

The rationale for any pathology-specific endpoint assessment including the intention to subgroup by pathological features, *a priori*, should be described, and the details of the pathology-specific endpoint quality assurance mechanism should be documented. A review of the cellular and molecular basis of the disease provides justification for the use of cellular and molecular pathology methodologies to determine trial eligibility or as part of the outcomes assessments and allows a reader to evaluate their suitability^{17,18}.

Methods: Participants, interventions, and outcomes

*SPIRIT-Path 9 Elaboration: Describe where the laboratory work will be carried out and the accreditation status of the laboratory/site.**

Explanation

The location of laboratory work (e.g. hospital, academic centre, contract research organisation, commercial laboratory or sponsor-approved provider) should be described, alongside the required accreditation status of the laboratory/site (e.g. Clinical Laboratory Improvement Amendments, Good Clinical Laboratory Practice, International Organization for Standardization). A description of the laboratory environment used for a study allows the generalisability of trial results to be judged; an intervention that requires highly specialised laboratory skills or methodologies may be less easily translated into routine practice. Accreditation of participating laboratory sites by a suitable external body provides confidence about the quality and standardisation of practice^{13,19}.

*SPIRIT-Path 10 Extension: Where trial-specific pathology reporting is required, document specimen pathway requirements and any requirement for pathologist 'double reporting' or central review.**

Explanation

Where study-specific pathology specimens are required for determination of trial eligibility, the details of all specimen pathways including organ/tissue type, specimen type (e.g. fine needle aspirate, needle core of specified gauge), specimen number and size, specimen fixation method, specimen processing details, and report turn-around-time should be documented. The precise

details of the specimen pathway allow sites to minimise sources of variability that can be introduced by non-standardised local protocols²⁰. Clear eligibility criteria are required to precisely define the study participants. Where histological criteria or other biospecimen-generated metrics form part of the eligibility criteria, the precise histological features or derived value meriting a specific diagnosis should be defined to minimise subjectivity²¹. If trial-specific reporting is required to determine eligibility i.e. anything in addition to that provided in the available routine clinical report, any specific requirement for central review and/or 'double' or 'consensus' reporting by more than two pathologists should be documented. Central review of specimens to assess eligibility or outcomes, which may involve 'double' or consensus reporting by a trial-specific group of pathologists, has been shown to reduce reporting variation and ensure participant suitability²².

*SPIRIT-Path 12 Extension: Outline the assessment methods and the timing of tissue sampling required for any pathology-specific outcomes.**

Explanation

The choice of an outcome derived from cellular or molecular analysis of a biospecimen should be explained in the context of the pathogenesis of the disease and the expected effect of any intervention. Where this is in the form of histological assessment, precise criteria for reporting and any use of central and/or 'double' reporting should be defined, as for eligibility assessment¹⁷. This improves the standardisation of assessment and allows the outcomes to be more fully understood. Defining the timing of specimen sampling with respect to interventions and outcome assessments within participant timelines mitigates against the biospecimen acquisition potentially biasing patient-reported outcomes and ensures standardisation of the interval between intervention and biological assessments during which cellular and molecular responses may evolve.

Methods: Data collection, management, and analysis

*SPIRIT-Path 18a (i) Extension: Describe any specific accreditation, training and performance assessment requirements for trial pathologists and laboratory staff.**

Explanation

The requirements for 'Good Clinical Practice' accreditation or equivalent for trial pathologists and laboratory staff and any additional accreditation/training required to deliver trial-specific data, for example, specific training to recognise and score histological features or immunohistochemical stains that may not be part of routine practice, should be documented. Standardised accreditation or trial-specific training for pathologists and laboratory staff reduces inter-individual variation and increase the reliability and reproducibility of trial-specific pathology activities^{16,19,23}. Discussions with regulators (e.g. European Medicines Agency, Medicines and Healthcare products Regulatory Agency UK, US Food and Drug Administration), where applicable, during trial design allow the incorporation within the protocol of standards required for or assisting regulatory approval of therapeutics or biomarkers, and these discussions should be documented as the rationale for mandated standards or training, where relevant.

*SPIRIT-Path 18a (ii) Extension: Describe the specimen documentation requirements and full specimen handling pathway.**

Explanation

Any regulatory advice that has informed on the design of protocols for the biospecimen pathway, for example, mandating a specific sampling schedule, should be considered and documented in the trial protocol. Incorporation of such advice within the trial protocol will aid subsequent regulatory approval. The requirement for documentation of sample details using a reporting standard method that is evidence-based or recommended by a professional body, such as the Bio-specimen Reporting for Improved Study Quality (BRISQ) guidelines (Tier 1 items) should be documented. The use of a standardised method for specimen detail recording provides transparency and quality assurance of

biospecimen use within a trial. Where not otherwise documented for assessment of eligibility or outcome, for example for future translational studies or biobanking, describe the protocol for sample collection including transport times if using fresh tissue/samples, handling, processing and storage or reference the inclusion of these details in a companion laboratory manual^{13,14,16,20,21}. A complete description of every stage of the specimen pathway ensures standardisation across centres and gives assurance to those undertaking any future studies on the biospecimens.

*SPIRIT-Path 18a (iii) Extension: Define any methods for specimen assessment by histochemical, immunohistochemical or molecular techniques.**

Explanation

The methods for any specimen assessment using qualitative or semi-quantitative evaluation of histochemistry, immunohistochemistry or in situ hybridisation should be defined, as should any methods for sample analysis using molecular pathology. Such standardisation of assessment increases the reliability of the data derived. A description of how pathology assessments are undertaken with reference to blinding to associated clinical data, treatment allocation and outcomes should be given. This ensures pathology assessments are made without conscious or unconscious bias¹⁶. Where applicable, outline the considerations of precision, accuracy, inter- and intra-observer variability of biomarker tests, and "estimates of uncertainty of measurement of laboratory tests" as defined in ISO 15189:2012²⁴. Careful consideration of biomarker test performance should allow an appropriate test to be chosen and increase the reliability of test data^{21,25}. If relevant, describe the digital pathology platform to be used, and define the methods to be used for digital image analysis or the use of artificial intelligence (AI) methods including details such as specific requirements for analytic 'regions of interest' and how algorithm performance will be evaluated, with reference to the SPIRIT-AI extension⁷. The methods should be documented in sufficient detail to allow analyses to be reproduced using the trial-specific images, aiding transparency and reproducibility.

*SPIRIT-Path 19 Extension: Describe any intended use of a digital pathology slide archive.**

Explanation

Any intended use of a digital pathology slide archive to facilitate central pathology review, translational research, or the development of AI-based analysis algorithms, should be documented. The nature of the governance arrangements in place for such an archive should also be recorded. An archive of whole-slide images allows increased value to be leveraged from the trial biospecimens and increases trial reproducibility and transparency by allowing review of eligibility and outcome assessments, where applicable^{26,27}. Maintenance of such archives for future use requires governance arrangements to be in place²⁶.

*SPIRIT-Path 20a Elaboration: Describe any methods to be used for adjusting for diagnostic drift during the trial.**

Explanation

Any statistical or other methods to be used for adjusting for diagnostic drift in clinical trials with prolonged recruitment or extended follow-ups should be described. Diagnostic drift occurs over longer periods as reporting patterns by pathologists change through experience or advances in understanding, and this should be considered at trial inception, depending on the proposed timescale of the trial¹⁶.

Ethics and dissemination

*SPIRIT-Path 26b Elaboration: Document enduring consent for future translational studies using tissue or any digital pathology images, if applicable.**

Explanation

If applicable, the intention to obtain enduring consent for future academic or commercial translational studies should be documented, with a clear statement of the likelihood of the need for future access to the specimen for clinical purposes and a clear statement of the procedure of how a patient can withdraw consent^{16,21}. Trial-specific biospecimens can be used for future research

studies if consent has been given although the same specimen, for example, a biopsy in a formalin-fixed paraffin-embedded tissue block, may be required for assessment within a clinical care pathway for the specific patient. The balance between the value of the specimen for research and the likelihood of the specimen being required for clinical care should form part of the consent process. Documentation of explicit consent for further studies involving genetic testing, computational evaluation of any digital pathology images and/or the use of linked study data, where appropriate, will allow the greatest future value from the gifted specimen.

*SPIRIT-Path 31c Extension: Describe the mechanism and timing for making digital pathology images available, if applicable.**

Explanation

Where digital images of tissue sections are used by trial pathologists to assess eligibility and/or outcome, the mechanism and timing for making these available should be described i.e. equivalent to making raw bioinformatic data available. The nature of proposed data sharing agreements and the continued governance and financial arrangements in place to maintain any accessible digital archive should also be documented. An available resource of histological images, annotated with trial data, will allow further understanding to be leveraged from the study biospecimen but requires maintenance. Where trial samples are to be retained for future studies, a description of how the availability of the samples for future use will be communicated, for example, availability to be documented within the reporting trial manuscript. Without the availability of consented biospecimens being disseminated, samples may not be utilised for suitable additional studies.

Appendices

*SPIRIT-Path 33 Elaboration: Specify the regulatory approvals required for clinical trial samples to be used in future work.**

Explanation

The regulatory approvals required for samples collected as part of the study protocol to become part of a separate biobank or retained by investigators in alternative resources for use in future work should be specified. If it is known that trial samples are to be submitted to an existing biobank, provide the name and evidence of biobank experience and certification. Identification of such requirements at trial inception allows arrangements in advance of the end of the study so that samples are available for future research and not at risk of disposal or archiving at participating sites under standard local practices.

Discussion

The SPIRIT-Path extension provides international consensus guidance about how cellular and molecular pathology content of clinical trials should be reported in trial protocols. Fourteen items have been agreed in the form of seven elaborations of the SPIRIT 2013 Statement and seven new extension items. The SPIRIT-Path extension was conceived as a means of both maximising the value of pathology content of clinical trial protocols and facilitating its execution²⁸ in the setting of precision medicine approaches to trials. Early engagement by trial protocol authors with pathologists and translational scientists helps to ensure that laboratory tests and processes are appropriate and achievable. Furthermore, the expertise of these individuals can be incorporated in trial protocols to enrich data collection and quality assure trial endpoints. The increased use of molecular pathology to inform patient selection and the ability to define distinct sub-groups with tissue biomarkers are important advances that improve the likelihood of success, particularly in drug evaluation studies^{29,30}. The increasing use of neoadjuvant treatments, including immuno-oncology agents, has made pathological complete response an important primary endpoint in these types of

trial³¹. Furthermore, the use of digital pathology, biomarker image analysis and the emergence of artificial intelligence algorithms in pathology will change the landscape of future clinical trial design²⁶. Engaging experts in the field will develop an increasing number of laboratory scientists and pathologists familiar with clinical trial design who are keen to work collaboratively for the benefit of patients. The principle of early engagement and involvement of specific stakeholders to enhance trial protocols is well-established, for example the vital contributions of patient stakeholders to study design, particularly where protocols include additional blood or tissue sampling. In addition, pathology laboratories often have biobanking infra-structure to host clinical trial tissue collections, which represents an important legacy for translational science. Funding for bio-resources is a moot point, as the activities are not without cost, but involving pathologists early in trial design will ensure these aspects are not overlooked and are adequately supported. The guidance does not define trial conduct but sets minimum standards for the documentation of cellular and molecular pathology trial protocol content. Adoption of these minimum standards will increase the transparency of clinical trials to allow results to be fully evaluated and compared, should increase the robustness of trials and improve interpretability and reproducibility.

The SPIRIT-Path guidance will have widespread applicability. Many therapeutic clinical trials, particularly in oncology, have eligibility criteria based upon a histological diagnosis. In such trials, all generated trial data and outputs, therefore, depend on the robustness of this pathological activity but no consensus guidance defining reporting of such a critical activity was previously available. Several SPIRIT-Path extensions relate to all aspects of both pathological eligibility decisions and any pathological endpoint assessment. Such assessments are important in oncological trials but also in trials of therapeutics for non-neoplastic disease, for example the critical histological assessment of disease activity in trials for the treatment of patients with ulcerative colitis³² or non-alcoholic fatty liver disease³³. The pertinent extension items specify the documentation of the requirements for the laboratories, pathologists and translational scientists undertaking the work, including details of all stages of any specimen pathway. Protocol authors may wish to have a section of the trial protocol

dedicated to pathology activities and may even consider including standard operating procedures (SOPs) within appendices.

The requirement to specify within the administrative sections the individuals responsible for the pathology content of the trial protocol will serve to allow trial protocol writers to engage with pathologists and scientists during protocol development. This should improve trial conduct using biological specimens and biomarkers and ensure that such activity within trials is appropriately recognised and resourced.

The consensus process generating the extension addressed the critical need for documentation of the requirements that relevant regulators have for evaluating different studies, for example, those using biomarkers. Without explicit documentation of the specimen and specimen pathway details that may be informed by discussion with regulators during trial design, subsequent regulatory evaluation of trial findings may be difficult and routes to approval and clinical use impossible.

The increasing use of digital images and related image analysis algorithms within pathology practice are also recognised by several extension items, both using whole-slide imaging as a tool to allow image sharing for consensus reporting and as a means of facilitating the computational evaluation of images to generate additional metrics. The application of artificial intelligence methodologies to large whole-slide image datasets may also be within the remit of the SPIRIT-AI extension⁷. The importance of both trial-specific biological specimens and histopathological images for future studies is reflected by guidance for specific documentation of explicit consent processes to allow this through increased data and specimen availability.

The study has the limitation that it necessarily involved highly motivated members of the clinical trials community that may not be fully representative. However, the generation of the first draft of candidate items was solely based on evidence gathered by a systematic review of all published guidance, since the CONSORT Statement in 1996³⁴. This was further expanded and modified by an international group of experts within the clinical trials community representing multiple territories

and stakeholder roles. The Delphi participants were chosen to more widely represent all roles within the international clinical trials community although the study was not designed to examine differences in opinion between participant groups and this cannot be formally excluded. The opportunity for a face-to-face consensus meeting requiring international travel of participants was not available due to the SARS-CoV-2 (COVID19) pandemic. However, multiple rounds of consultation in advance of an online meeting that was available for view and comment by those unable to attend virtually allowed complete consensus about the final form of the SPIRIT-Path extension to be reached.

We believe that the SPIRIT-Path extension is the necessary first step towards an approach to pathology that fully meets the needs of precision medicine. Next-generation pathology will be enabled by the application of novel biomarker tests in quality assured tissue, digitisation of morpho-molecular information, the application of computer vision technology and artificial intelligence, and integration with whole-genome analysis, including the identification of actionable mutations and assessment of tumour mutational burden.

Search strategy and selection criteria

In the prior systematic review of published guidance⁹, free-text terms such as '(histolo*; OR patholo*)' AND '(checklist; OR guideline; OR recommendation)' AND '(clinical trial; OR protocol)', along with equivalent controlled vocabulary terms, were used in the search through the databases of MEDLINE (Ovid), EMBASE (Ovid) and Cochrane Library. Additional search terms such as 'biomarker*', 'molecular diagnos*', 'practice guid*', 'study design' were also applied across the MEDLINE and EMBASE databases. Web searches on Google and Google Scholar were performed using the advanced search function, with the keywords '(Pathology; OR Histology; OR Biomarkers)' AND '(Guideline; OR Checklist)' AND 'Clinical trial'. Only the first 3 pages (30 results) from each internet search were screened. Of the 10,184 records screened and 199 full-text articles reviewed, only 40 guidance resources met the eligibility criteria for inclusion.

Author contributions

TJK and MR had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. TJK and MR are co-chairs of the SPIRIT-Path Group. All authors had full access to all the data reported in the study and have final responsibility for the decision to submit for publication. Concept and design – All authors. Acquisition, analysis and interpretation of data – all authors. Drafting of the manuscript – TJK, MR, SJL. Revision of the manuscript – all authors.

Declaration of interests

IL is a current employee of the NCRI that supports the work of the CMPath initiative and the SPIRIT-Path Project, DJH receives administrative support for chairing CMPath. All other authors have no conflicts of interest to declare.

Data sharing

Aggregated participant responses to the Delphi survey are presented in appendix pp 3-12. Individual or attributed participant responses are not available.

Role of the funding source

The study/project funders/sponsors had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

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References

- 1 Chan A-W, Song F, Vickers A, *et al.* Increasing value and reducing waste: addressing inaccessible research. *Lancet* 2014; **383**: 257–66.
- 2 Ioannidis JPA, Greenland S, Hlatky MA, *et al.* Research: increasing value, reducing waste 2. *Lancet* 2014; **383**: 166–75.
- 3 Chan A-W, Tetzlaff JM, Altman DG, *et al.* SPIRIT 2013 Statement: Defining Standard Protocol Items for Clinical Trials. *Ann Intern Med* 2013; **158**: 200–7.
- 4 Chan A-W, Tetzlaff JM, Gøtzsche PC, *et al.* SPIRIT 2013 explanation and elaboration: guidance for protocols of clinical trials. *BMJ* 2013; **346**: e7586.
- 5 Calvert M, Kyte D, Mercieca-Bebber R, *et al.* Guidelines for Inclusion of Patient-Reported Outcomes in Clinical Trial Protocols: The SPIRIT-PRO Extension. *JAMA* 2018; **319**: 483–94.
- 6 Porcino AJ, Shamseer L, Chan A-W, *et al.* SPIRIT extension and elaboration for n-of-1 trials: SPENT 2019 checklist. *BMJ* 2020; **368**: m122.
- 7 Cruz Rivera S, Liu X, Chan A-W, Denniston AK, Calvert MJ. Guidelines for clinical trial protocols for interventions involving artificial intelligence: the SPIRIT-AI extension. *Nature Medicine* 2020; **26**: 1351–63.
- 8 Spatz A, Ruiter DJ, Busch C, Theodorovic I, Oosterhuis JW. The role of the EORTC pathologist in clinical trials: achievements and perspectives. European Organisation for Research and Treatment of Cancer. *Eur J Cancer* 2002; **38 Suppl 4**: S120-124.
- 9 Lim SJ, Gurusamy K, O'Connor D, *et al.* Recommendations for cellular and molecular pathology input into clinical trials: a systematic review and meta-aggregation. *The Journal of Pathology: Clinical Research* 2021; **7**: 191–202.
- 10 Lim SJ. The SPIRIT-Path Extension (Updated). Open Science Framework [Internet. 2020 <https://osf.io/jeqtx>.
- 11 Humphrey-Murto S, Varpio L, Gonsalves C, Wood TJ. Using consensus group methods such as Delphi and Nominal Group in medical education research. *Medical Teacher* 2017; **39**: 14–9.
- 12 Tsihlaki A, O'Brien K, Johal A, *et al.* Development of a core outcome set for orthodontic trials using a mixed-methods approach: protocol for a multicentre study. *Trials* 2017; **18**: 366.
- 13 Nagtegaal ID, West NP, Krieken JHJ van, Quirke P. Pathology is a necessary and informative tool in oncology clinical trials. *The Journal of Pathology* 2014; **232**: 185–9.

- 14 National Cancer Institute. NCI Best Practices for Biospecimen Resources. 2016.
- 15 Rees G, Salto-Tellez M, Lee JL, *et al.* Training and accreditation standards for pathologists undertaking clinical trial work. *The Journal of Pathology: Clinical Research* 2019; **5**: 100.
- 16 Robinson M, James J, Thomas G, *et al.* Quality assurance guidance for scoring and reporting for pathologists and laboratories undertaking clinical trial work. *The Journal of Pathology: Clinical Research* 2019; **5**: 91.
- 17 Peppercorn J, Shapira I, Collyar D, *et al.* Ethics of Mandatory Research Biopsy for Correlative End Points Within Clinical Trials in Oncology. *Journal of Clinical Oncology* 2010; **28**: 2635.
- 18 Makhlof H, Watson MA, Lankes HA, *et al.* Toward Improving Practices for Submission of Diagnostic Tissue Blocks for National Cancer Institute Clinical Trials. *Am J Clin Pathol* 2020; **153**: 149–55.
- 19 Sarzotti-Kelsoe M, Cox J, Cleland N, *et al.* Evaluation and recommendations on good clinical laboratory practice guidelines for phase I-III clinical trials. *PLoS Med* 2009; **6**: e1000067.
- 20 LaBaer J. Improving International Research with Clinical Specimens: 5 Achievable Objectives. *J Proteome Res* 2012; **11**: 5592–601.
- 21 Hall JA, Daidone MG, Peters GJ, Harbeck N, Lacombe D, Sleijfer S. Integrating collection of biospecimens in clinical trials: the approach of the European organization for research and treatment of cancer. *Biopreserv Biobank* 2011; **9**: 181–6.
- 22 Vujančić GM, Sandstedt B, Kelsey A, Sebire NJ. Central pathology review in multicenter trials and studies. *Cancer* 2009; **115**: 1977–83.
- 23 Röcken C. Quality assurance in clinical trials—the role of pathology. *Virchows Arch* 2016; **468**: 83–92.
- 24 Orlando L, Viale G, Bria E, *et al.* Discordance in pathology report after central pathology review: Implications for breast cancer adjuvant treatment. *The Breast* 2016; **30**: 151–5.
- 25 Dancey JE, Dobbin KK, Groshen S, Jessup JM, Hruszkewycz AH, Koehler M. Guidelines for the development and incorporation of biomarker studies in early clinical trials of novel agents. *Clin Cancer Res* 2010; **16**: 1745–55.
- 26 Pell R, Oien K, Robinson M, *et al.* The use of digital pathology and image analysis in clinical trials. *The Journal of Pathology: Clinical Research* 2019; **5**: 81–90.
- 27 Mroz P, Parwani AV, Kulesza P. Central Pathology Review for Phase III Clinical Trials: The Enabling Effect of Virtual Microscopy. *Archives of Pathology & Laboratory Medicine* 2013; **137**: 492–5.
- 28 Provenzano E, Driskell OJ, O'Connor DJ, *et al.* The important role of the histopathologist in clinical trials: challenges and approaches to tackle them. *Histopathology* 2020; **76**: 942–9.
- 29 Turner NC, Kingston B, Kilburn LS, *et al.* Circulating tumour DNA analysis to direct therapy in advanced breast cancer (plasmaMATCH): a multicentre, multicohort, phase 2a, platform trial. *The Lancet Oncology* 2020; **21**: 1296–308.

- 30 Middleton G, Fletcher P, Popat S, *et al.* The National Lung Matrix Trial of personalized therapy in lung cancer. *Nature* 2020; **583**: 807–12.
- 31 Provenzano E, Bossuyt V, Viale G, *et al.* Standardization of pathologic evaluation and reporting of postneoadjuvant specimens in clinical trials of breast cancer: recommendations from an international working group. *Mod Pathol* 2015; **28**: 1185–201.
- 32 Cooney RM, Warren BF, Altman DG, Abreu MT, Travis SP. Outcome measurement in clinical trials for ulcerative colitis: towards standardisation. *Trials* 2007; **8**: 17.
- 33 Sanyal AJ, Brunt EM, Kleiner DE, *et al.* Endpoints and clinical trial design for nonalcoholic steatohepatitis. *Hepatology* 2011; **54**: 344–53.
- 34 Begg C, Cho M, Eastwood S, *et al.* Improving the quality of reporting of randomized controlled trials. The CONSORT statement. *JAMA* 1996; **276**: 637–9.

Guidelines for cellular and molecular pathology content in clinical trial protocols: the SPIRIT-Path extension

Timothy J. Kendall, MD* ; Max Robinson, BDS* ; Daniel J. Brierley, BDS; Shujing Jane Lim, MD; Daniel J. O'Connor, MD; Professor Abeer M. Shaaban, MD; Ian Lewis, PhD; Professor An-Wen Chan, MD; Professor David J. Harrison, MD; for the SPIRIT-Path Group.

Author Affiliations: University of Edinburgh Centre for Inflammation Research, University of Edinburgh, Edinburgh, United Kingdom (Kendall); Department of Cellular Pathology, Newcastle upon Tyne Hospitals NHS Foundation Trust, Newcastle, United Kingdom (Robinson, Lim); Unit of Oral and Maxillofacial Pathology, University of Sheffield, Sheffield, United Kingdom (Brierley); The Medicines and Healthcare products Regulatory Agency, London, United Kingdom (O'Connor); Queen Elizabeth Hospital Birmingham and University of Birmingham, Birmingham, United Kingdom (Shaaban); National Cancer Research Institute, London, United Kingdom (Lewis); Women's College Research Institute, Department of Medicine, University of Toronto, Toronto, Ontario, Canada (Chan); University of St Andrews, St Andrews, United Kingdom (Harrison)

*These authors contributed equally.

Corresponding author: Timothy J. Kendall, University of Edinburgh Centre for Inflammation Research, Queen's Medical Research Institute, 47 Little France Crescent, Edinburgh EH16 4TJ, United Kingdom (Tim.Kendall@ed.ac.uk).

Summary

The SPIRIT 2013 Statement provides evidence-based recommendations for the minimum content of clinical trial protocols. Assessment of biospecimens is often required for trial eligibility or as part of outcome evaluation, and precision molecular approaches are increasingly used in trial design. However, cellular and molecular pathology practices within trials have neither been codified nor formalised. We developed international consensus reporting guidelines for cellular and molecular pathology content in clinical trial protocols (the SPIRIT-Path Extension) using an international Delphi process assessing candidate items generated from a prior systematic review, followed by an expert consensus meeting. 74 individuals from five continents responded, including clinicians, statisticians, laboratory scientists, patient advocates, funders, industry representatives, journal editors, and regulators. The SPIRIT-Path guidelines recommend 14 additional items, 7 extensions to the SPIRIT checklist and 7 elaborations, that should be addressed in trial protocols with pathology content alongside the SPIRIT 2013 Statement items. SPIRIT-Path recommends that protocols should document the individuals, processes, and standards for all cellular and molecular pathology components of the trial protocol, including all stages of the specimen pathway, any digital pathology methods, and with specific consideration of the value of trial data and tissue for additional translational studies.

Introduction

The clinical trial protocol is an essential document that describes the rationale and conduct of the proposed research. The document must contain sufficient information to allow review when seeking funding, support the safe and optimal conduct of the study against the trial objectives, and allow subsequent results to be evaluated and compared with other trials^{1,2}. Despite the importance of trial protocols, their quality and content are known to be variable. The SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) 2013 Statement provides evidence-based recommendations for the minimum content of clinical trial protocols to address this variability^{3,4}.

The statement is widely endorsed by medicines developers, academia, regulators and medical journals.

Extensions to the SPIRIT 2013 Statement have been produced to address specific trial protocol elements that are not addressed fully by application of the original guidelines; to date, these relate to patient-reported outcomes⁵, n-of-one trials⁶, and trials evaluating artificial intelligence interventions⁷. A SPIRIT extension item is an additional checklist item that addresses an aspect of protocol content that is not adequately covered by the SPIRIT 2013 Statement, as judged by available evidence and subject-matter expert opinion; a SPIRIT elaboration item is an elaboration of an existing SPIRIT item as it applies to a particular subject area⁵.

Pathological assessment including confirmation of diagnosis is required for determining eligibility or outcome assessment in therapeutic trials of specific conditions, particularly in oncology but also in therapeutic trials in non-neoplastic diseases, for example those with an inflammatory or immune-mediated aetiology or with fibrotic sequelae, and is still regarded as the gold standard⁸. Such clinical trials increasingly use precision molecular approaches in their design, but these do not always capitalise on the richness of data available from full pathological assessment. Despite such technological advances, the crucial decision to determine participant eligibility often relies on traditional subjective assessment of tissue sections by a pathologist. Such practice has neither been codified nor formalised and does not yet fully integrate novel molecular analyses.

SPIRIT-Path is a fully international project coordinated by the UK National Cancer Research Institute's Cellular and Molecular Pathology Initiative (NCRI CMPath) and supported by the SPIRIT group to extend the SPIRIT 2013 Statement, where needed, for trials that include cellular and molecular pathology protocol content. Here we describe the SPIRIT-Path guideline development and provide a checklist with explanations. The extension offers guidance to authors of clinical trial protocols that include pathology activities to ensure all possible steps, including aspects of specimen handling and reporting, are identified at trial inception. Investigators should consider documenting

the pathology methods in a dedicated section of the trial protocol. This will allow trial protocols to comprehensively address cellular and molecular pathology aspects, ensuring adequate skills and resources are available at trial commencement to facilitate the smooth running of laboratory-based components of the trial and fully leverage the value of biospecimens for translational research.

Methods

The SPIRIT-Path project was conceived by members of NCRI CMPath Clinical Trials workstream in May 2019. The SPIRIT-Path Core Group (TJK, MR, SJL, DJB, DOC, AMS, IL, DJH) responsible for the project was established in June 2019 and the SPIRIT-Path International Advisory Group (AWC and all other SPIRIT-Path Ggroup members, appendix pp 25) was assembled shortly afterwards, with the support of the SPIRIT group, to include expert representation from multiple territories and all stakeholder groups in the clinical trials community. A prior systematic review of published guidance was used to identify candidate items was undertaken from January to April 2020⁹. The SPIRIT-Path extension was registered as reporting guidelines under development with the EQUATOR Network in May 2020 and was developed in accordance with the EQUATOR Network's methodology.

Ethical considerations

The project was undertaken by following the UK Research Integrity Office's (UKRIO) Code of Practice for Research and the Universities UK (UUK) Concordat to Support Research Integrity adopted as the University of Edinburgh's Research Integrity framework and was assessed before study commencement using the UKRIO checklist for good practice in research in advance as a peer opinion study. Information was given to Delphi participants in the introductory page of the survey, and electronic informed consent, including for disclosure of participant name and affiliation at publication, was obtained following General Data Protection Regulation best practices and before survey completion (appendix pp 1). Information was given to consensus meeting participants in advance, and consent for the recording of the meeting was obtained at the start of the meeting and before beginning recording.

Candidate item generation

A systematic review to identify and synthesise existing recommendations specific to pathology practice in clinical trials for implementation in trial protocol design published between 1st January 1996 and 13th January 2020 has previously been undertaken⁹. In the prior review, resources were eligible for inclusion if they contained - (1) guidance (in the form of guidelines or expert recommendations) and/or a checklist, which are (2) pathology-related, with (3) content relevant to clinical trial protocols or that could influence a clinical trial protocol design from a pathology perspective. There were no restrictions by language or publication type. The full search strategies for all database and web searches are available in the pre-registered protocol¹⁰. ~~Free text terms such as '(histolo*; OR patholo*)' AND '(checklist; OR guideline; OR recommendation)' AND '(clinical trial; OR protocol)', along with equivalent controlled vocabulary terms, were used in the search through the databases of MEDLINE (Ovid), EMBASE (Ovid) and Cochrane Library. Additional search terms such as 'biomarker*', 'molecular diagnos*', 'practice guid*', 'study design' were also applied across the MEDLINE and EMBASE databases. Web searches on Google and Google Scholar were performed using the advanced search function, with the keywords '(Pathology; OR Histology; OR Biomarkers)' AND '(Guideline; OR Checklist)' AND 'Clinical trial'. Only the first 3 pages (30 results) from each internet search were screened. Of the 10,184 records screened and 199 full text articles reviewed, only 40 guidance resources met the eligibility criteria for inclusion.~~ The Core Group and International Advisory Group members and UK Clinical Trials Unit leads were consulted during the review process to identify any additional sources of guidance.

Verbatim extracted guidance was mapped to the SPIRIT 2013 Statement and a provisional list of candidate items was generated by the Core Group. The final list of 48 candidate items was produced after consultation with the International Advisory Group members allowing item revision or addition (appendix pp 3-12).

International Delphi Exercise

Participants

The Core Group members selected participants after consultation with the International Advisory Group members to create an “expert” panel in multiple territories across all stakeholder roles in the clinical trials community. In line with recommendations regarding how to select “experts”¹¹, it was felt those selected were most knowledgeable in this area, representative of the area of inquiry and had considerable practical experience to warrant them “experts”. Participants were also selected to provide international representation from many territories. As those responsible for developing the candidate items, the Core Group members did not provide responses in the Delphi process to minimise potential bias. Characteristics of the 74 Delphi panelists (appendix pp 1-2) were recorded during the process and are summarised in appendix pp 13-14. Participants included clinicians, clinical trialists, statisticians, trials methodologists, trials and data managers, clinical laboratory scientists, patient advocates, funders, industry representatives, journal editors, and regulators from Africa, Asia, Australasia, Europe and North America.

Rating

Participants were asked to rate the importance of items on a nine-point Likert-type item scale, where ‘9’ represented ‘critical’ and ‘1’ represented ‘not important’. Participants were able to use free-text boxes to justify their scores or offer other items that were not included as candidates.

An item was defined as ‘consensus-in’ when >70% of participants scored the item as ‘7-9 (critical)’ with <15% scoring ‘1-3 (not important)’. An item was classified as ‘consensus-out’ when >70% of participants scored an item ‘1-3’ and <15% of participants scored it ‘7-9’. All other combinations were considered to be ‘no consensus’, in accordance with previous research that used similar nine- or ten-point scales¹².

Procedure

A minimum of two rounds was chosen to allow participants to reflect and change their scores between rounds. A third round was not required because of the level of agreement reached by the end of the second round.

Three members of the SPIRIT-Path Core Group (TJK, MR, DJB) piloted the first round and suggested slight amendments to the instructions and wording of some items to ensure they aligned with scoring on a rating scale.

All communication between the researchers and Delphi participants used private, individual email addresses so participants remained anonymous to one another. The Delphi was conducted via Checkbox (Checkbox Survey Inc, Watertown, MA, USA) with links to the Delphi provided in the preparatory emails. For Round One (17th June 2020), participants were given instructions, a consent form, and the items to rate. Participants were asked to complete the survey by 15th July 2020 and reminder emails were sent to non-responders.

Round Two (10th August 2020) of the Delphi was sent only to those participants who responded to Round One. Participants were advised which items did not reach consensus in Round One and which had been amended based on feedback and asked to re-rate these items.. Participants were also given information from the previous round including their score for each item and the median panel score based on all participants' scores. They were informed that their scores from Round One would be carried forward for any item for which a new score was not returned and asked to complete the survey by 7th September 2020. Reminder emails were sent to non-responders.

Analysis

In Rounds One and Two, response rate, median score and item consensus scores were calculated. Data were analysed in Excel. In addition, free text comments were reviewed by the SPIRIT-Path Core Group to determine if items needed amendment or additional items required inclusion.

Rationalisation and checklist summary consensus meeting

After the final round of the Delphi exercise, 'consensus-in' items were re-mapped to the SPIRIT 2013 Statement and grouped by theme. For each item, an assessment of the need for an extension or elaboration to the SPIRIT 2013 Statement was made by the Core Group. Items within a theme were combined and draft wording for the extension or elaboration checklist item and explanatory text for each thematic grouping were produced.

The draft document was remotely assessed by the International Advisory Group through two circulations in October 2020, with revisions made after each circulation. After revisions following the second circulation, the candidate SPIRIT-Path items were circulated in advance of a virtual consensus meeting on 4th November 2020, to which all Core Group and International Advisory Group members were invited. The meeting was recorded with the informed consent of participants to allow those unable to attend to contribute. There was an opportunity to discuss items that did not reach consensus and, for each 'consensus-in' item, the need for either an extension or elaboration was considered. The proposed thematic groupings of each item were discussed in addition to the wording of both the checklist item and the explanatory text.

Following the meeting a final draft of the checklist items and explanatory text was produced by the Core Group. This was circulated for a final time around the International Advisory Group and all members agreed with the wording.

Results

196 invitations to participate in Round One of the Delphi exercise were sent (156 individuals and 40 organisations). 74 individuals consented to participate with 66 fully completing Round One of the Delphi in full; 42 of 48 items reached 'consensus-in' (appendix pp 3-12) while the remainder (items #6, #7, #8, #19, #37 and #42) did not reach consensus. After modification of items without consensus, invitations for Round Two were sent only to those participants who responded in Round

One. 46 participants decided to amend their scores from Round One with 44 participants completing Round Two in full; those who did not respond had their Round One scores carried forward into Round Two. Four of the six remaining modified items reached 'consensus-in' (appendix pp 3-12); no consensus was reached for two items (#7 and #42).

SPIRIT-Path Checklist Items and Explanation

The post-Delphi rationalisation process and consensus meeting merged the 46 agreed items by theme, mapped to the SPIRIT 2013 statement (Figure 1 and appendix pp 15-24). The SPIRIT-Path extension recommends that an additional 14 items (seven extensions and seven elaborations, Table 1) that should be addressed in trial protocols with pathology content alongside the SPIRIT 2013 Statement items and other SPIRIT extensions where relevant. These items were considered to be of sufficient significance to trials with any cellular and molecular pathology content that they should be explicitly addressed in trial protocols. All members of the International Advisory Group agreed with the inclusion of these extension items in this form.

Some items will only apply to clinical trials where there is a requirement for trial-specific specimen activity outside of the routine diagnostic pathway, including the acquisition of trial-specific samples or review/analysis of historical samples; these items are indicated by an asterisk (*).

Administrative information

SPIRIT-Path 5a Elaboration: Specify the individual(s) responsible for pathology content of the trial protocol.

Explanation

The individuals responsible for developing protocol content should be specified. This includes those responsible for protocol content regarding pathology reporting methodology, pathology-specific quality assurance, biospecimen institutional release, movement across trial sites, and archiving and biobanking, where applicable. The documentation of the contributions of specific authors to the trial protocol with affiliations increases transparency, helps identify potential conflicts of interest, and

formally recognises the contribution of the pathologists and laboratory scientists to trial development. For protocols describing trial-specific pathology reporting, it is helpful to document the pathologists and translational scientists who have designed or verified the tissue pathway from sample acquisition to analysis to ensure that the ‘turn-around times’ for scoring and reporting trial data are feasible. Specific documentation of the author responsible for the biospecimen pathway and reporting provides accountability and evidence of consultation with appropriate professionals in protocol design^{13,14}. If there is no involvement of protocol authors with pathology expertise, then a reason should be provided.

SPIRIT-Path 5d Elaboration: Specify how pathology activities and roles are organised in the trial.

Explanation

The organisation of all items related to pathology within the trial should be specified, detailing the responsibilities of the stakeholders. The composition/operation of the Pathology Steering Group or Molecular Tumour Board, if deemed relevant, should be documented, and how representation from these groups and their operation is integrated within the Trial Management Group should be clearly explained. When pathology-based biomarkers are critical to patient recruitment and/or if pathology complete response is the primary outcome measure, a pathologist and/or translational scientist may be included in the Data Monitoring Committee and their role within this committee should be documented. It should be confirmed in the protocol that contractual agreements will be in place between the trial sponsor and the participating centre laboratories concerning the exchange of samples. This information ensures that the required cellular and molecular pathology expertise and responsibilities are clearly defined at trial inception, where applicable, and outlines how trial-specific pathology activity is integrated into overall trial management to maximise the contribution to trial operation^{13,15,16}. It allows readers to understand and evaluate the relevant expertise of those responsible for the pathology aspects of the trial.

Introduction

SPIRIT-Path 6a Elaboration: Describe the pathogenesis of the disease and rationale for any pathology-specific inclusion criteria or endpoints.

Explanation

The cellular and molecular basis of the disease should be described, with justification of the rationale for incorporating any trial-specific biomarkers and any pathology-specific criteria for recruitment. The analytical performance of any laboratory assays (proprietary or laboratory-developed tests) should be described; where these are not known (e.g. if the development of an assay is part of the study), then an evidence-based prediction of performance should be described.

The rationale for any pathology-specific endpoint assessment including the intention to subgroup by pathological features, *a priori*, should be described, and the details of the pathology-specific endpoint quality assurance mechanism should be documented. A review of the cellular and molecular basis of the disease provides justification for the use of cellular and molecular pathology methodologies to determine trial eligibility or as part of the outcomes assessments and allows a reader to evaluate their suitability^{17,18}.

Methods: Participants, interventions, and outcomes

*SPIRIT-Path 9 Elaboration: Describe where the laboratory work will be carried out and the accreditation status of the laboratory/site. **

Explanation

The location of laboratory work (e.g. hospital, academic centre, contract research organisation, commercial laboratory or sponsor-approved provider) should be described, alongside the required accreditation status of the laboratory/site (e.g. Clinical Laboratory Improvement Amendments, Good Clinical Laboratory Practice, International Organization for Standardization). A description of the laboratory environment used for a study allows the generalisability of trial results to be judged; an intervention that requires highly specialised laboratory skills or methodologies may be less easily

translated into routine practice. Accreditation of participating laboratory sites by a suitable external body provides confidence about the quality and standardisation of practice^{13,19}.

*SPIRIT-Path 10 Extension: Where trial-specific pathology reporting is required, document specimen pathway requirements and any requirement for pathologist 'double reporting' or central review.**

Explanation

Where study-specific pathology specimens are required for determination of trial eligibility, the details of all specimen pathways including organ/tissue type, specimen type (e.g. fine needle aspirate, needle core of specified gauge), specimen number and size, specimen fixation method, specimen processing details, and report turn-around-time should be documented. The precise details of the specimen pathway allow sites to minimise sources of variability that can be introduced by non-standardised local protocols²⁰. Clear eligibility criteria are required to precisely define the study participants. Where histological criteria or other biospecimen-generated metrics form part of the eligibility criteria, the precise histological features or derived value meriting a specific diagnosis should be defined to minimise subjectivity²¹. If trial-specific reporting is required to determine eligibility i.e. anything in addition to that provided in the available routine clinical report, any specific requirement for central review and/or 'double' or 'consensus' reporting by more than two pathologists should be documented. Central review of specimens to assess eligibility or outcomes, which may involve 'double' or consensus reporting by a trial-specific group of pathologists, has been shown to reduce reporting variation and ensure participant suitability²².

*SPIRIT-Path 12 Extension: Outline the assessment methods and the timing of tissue sampling required for any pathology-specific outcomes.**

Explanation

The choice of an outcome derived from cellular or molecular analysis of a biospecimen should be explained in the context of the pathogenesis of the disease and the expected effect of any intervention. Where this is in the form of histological assessment, precise criteria for reporting and

any use of central and/or 'double' reporting should be defined, as for eligibility assessment¹⁷. This improves the standardisation of assessment and allows the outcomes to be more fully understood. Defining the timing of specimen sampling with respect to interventions and outcome assessments within participant timelines mitigates against the biospecimen acquisition potentially biasing patient-reported outcomes and ensures standardisation of the interval between intervention and biological assessments during which cellular and molecular responses may evolve.

Methods: Data collection, management, and analysis

*SPIRIT-Path 18a (i) Extension: Describe any specific accreditation, training and performance assessment requirements for trial pathologists and laboratory staff.**

Explanation

The requirements for 'Good Clinical Practice' accreditation or equivalent for trial pathologists and laboratory staff and any additional accreditation/training required to deliver trial-specific data, for example, specific training to recognise and score histological features or immunohistochemical stains that may not be part of routine practice, should be documented. Standardised accreditation or trial-specific training for pathologists and laboratory staff reduces inter-individual variation and increase the reliability and reproducibility of trial-specific pathology activities^{16,19,23}. Discussions with regulators (e.g. European Medicines Agency, Medicines and Healthcare products Regulatory Agency UK, US Food and Drug Administration), where applicable, during trial design allow the incorporation within the protocol of standards required for or assisting regulatory approval of therapeutics or biomarkers, and these discussions should be documented as the rationale for mandated standards or training, where relevant.

*SPIRIT-Path 18a (ii) Extension: Describe the specimen documentation requirements and full specimen handling pathway.**

Explanation

Any regulatory advice that has informed on the design of protocols for the biospecimen pathway, for example, mandating a specific sampling schedule, should be considered and documented in the trial protocol. Incorporation of such advice within the trial protocol will aid subsequent regulatory approval. The requirement for documentation of sample details using a reporting standard method that is evidence-based or recommended by a professional body, such as the Bio-specimen Reporting for Improved Study Quality (BRISQ) guidelines (Tier 1 items) should be documented. The use of a standardised method for specimen detail recording provides transparency and quality assurance of biospecimen use within a trial. Where not otherwise documented for assessment of eligibility or outcome, for example for future translational studies or biobanking, describe the protocol for sample collection including transport times if using fresh tissue/samples, handling, processing and storage or reference the inclusion of these details in a companion laboratory manual^{13,14,16,20,21}. A complete description of every stage of the specimen pathway ensures standardisation across centres and gives assurance to those undertaking any future studies on the biospecimens.

*SPIRIT-Path 18a (iii) Extension: Define any methods for specimen assessment by histochemical, immunohistochemical or molecular techniques.**

Explanation

The methods for any specimen assessment using qualitative or semi-quantitative evaluation of histochemistry, immunohistochemistry or in situ hybridisation should be defined, as should any methods for sample analysis using molecular pathology. Such standardisation of assessment increases the reliability of the data derived. A description of how pathology assessments are undertaken with reference to blinding to associated clinical data, treatment allocation and outcomes should be given. This ensures pathology assessments are made without conscious or unconscious bias¹⁶. Where applicable, outline the considerations of precision, accuracy, inter- and intra-observer

variability of biomarker tests, and "estimates of uncertainty of measurement of laboratory tests" as defined in ISO 15189:2012²⁴. Careful consideration of biomarker test performance should allow an appropriate test to be chosen and increase the reliability of test data^{21,25}. If relevant, describe the digital pathology platform to be used, and define the methods to be used for digital image analysis or the use of artificial intelligence (AI) methods including details such as specific requirements for analytic 'regions of interest' and how algorithm performance will be evaluated, with reference to the SPIRIT-AI extension⁷. The methods should be documented in sufficient detail to allow analyses to be reproduced using the trial-specific images, aiding transparency and reproducibility.

*SPIRIT-Path 19 Extension: Describe any intended use of a digital pathology slide archive.**

Explanation

Any intended use of a digital pathology slide archive to facilitate central pathology review, translational research, or the development of AI-based analysis algorithms, should be documented. The nature of the governance arrangements in place for such an archive should also be recorded. An archive of whole-slide images allows increased value to be leveraged from the trial biospecimens and increases trial reproducibility and transparency by allowing review of eligibility and outcome assessments, where applicable^{26,27}. Maintenance of such archives for future use requires governance arrangements to be in place²⁶.

*SPIRIT-Path 20a Elaboration: Describe any methods to be used for adjusting for diagnostic drift during the trial.**

Explanation

Any statistical or other methods to be used for adjusting for diagnostic drift in clinical trials with prolonged recruitment or extended follow-ups should be described. Diagnostic drift occurs over longer periods as reporting patterns by pathologists change through experience or advances in understanding, and this should be considered at trial inception, depending on the proposed timescale of the trial¹⁶.

Ethics and dissemination

*SPIRIT-Path 26b Elaboration: Document enduring consent for future translational studies using tissue or any digital pathology images, if applicable.**

Explanation

If applicable, the intention to obtain enduring consent for future academic or commercial translational studies should be documented, with a clear statement of the likelihood of the need for future access to the specimen for clinical purposes and a clear statement of the procedure of how a patient can withdraw consent^{16,21}. Trial-specific biospecimens can be used for future research studies if consent has been given although the same specimen, for example, a biopsy in a formalin-fixed paraffin-embedded tissue block, may be required for assessment within a clinical care pathway for the specific patient. The balance between the value of the specimen for research and the likelihood of the specimen being required for clinical care should form part of the consent process. Documentation of explicit consent for further studies involving genetic testing, computational evaluation of any digital pathology images and/or the use of linked study data, where appropriate, will allow the greatest future value from the gifted specimen.

*SPIRIT-Path 31c Extension: Describe the mechanism and timing for making digital pathology images available, if applicable.**

Explanation

Where digital images of tissue sections are used by trial pathologists to assess eligibility and/or outcome, the mechanism and timing for making these available should be described i.e. equivalent to making raw bioinformatic data available. The nature of proposed data sharing agreements and the continued governance and financial arrangements in place to maintain any accessible digital archive should also be documented. An available resource of histological images, annotated with trial data, will allow further understanding to be leveraged from the study biospecimen but requires maintenance. Where trial samples are to be retained for future studies, a description of how the

availability of the samples for future use will be communicated, for example, availability to be documented within the reporting trial manuscript. Without the availability of consented biospecimens being disseminated, samples may not be utilised for suitable additional studies.

Appendices

*SPIRIT-Path 33 Elaboration: Specify the regulatory approvals required for clinical trial samples to be used in future work.**

Explanation

The regulatory approvals required for samples collected as part of the study protocol to become part of a separate biobank or retained by investigators in alternative resources for use in future work should be specified. If it is known that trial samples are to be submitted to an existing biobank, provide the name and evidence of biobank experience and certification. Identification of such requirements at trial inception allows arrangements in advance of the end of the study so that samples are available for future research and not at risk of disposal or archiving at participating sites under standard local practices.

Discussion

The SPIRIT-Path extension provides international consensus guidance about how cellular and molecular pathology content of clinical trials should be reported in trial protocols. Fourteen items have been agreed in the form of seven elaborations of the SPIRIT 2013 Statement and seven new extension items. The SPIRIT-Path extension was conceived as a means of both maximising the value of pathology content of clinical trial protocols and facilitating its execution²⁸ in the setting of precision medicine approaches to trials. Early engagement by trial protocol authors with pathologists and translational scientists helps to ensure that laboratory tests and processes are appropriate and achievable. Furthermore, the expertise of these individuals can be incorporated in trial protocols to enrich data collection and quality assure trial endpoints. The increased use of molecular pathology to inform patient selection and the ability to define distinct sub-groups with

tissue biomarkers are important advances that improve the likelihood of success, particularly in drug evaluation studies^{29,30}. The increasing use of neoadjuvant treatments, including immuno-oncology agents, has made pathological complete response an important primary endpoint in these types of trial³¹. Furthermore, the use of digital pathology, biomarker image analysis and the emergence of artificial intelligence algorithms in pathology will change the landscape of future clinical trial design²⁶. Engaging experts in the field will develop an increasing number of laboratory scientists and pathologists familiar with clinical trial design who are keen to work collaboratively for the benefit of patients. The principle of early engagement and involvement of specific stakeholders to enhance trial protocols is well-established, for example the vital contributions of patient stakeholders to study design, particularly where protocols include additional blood or tissue sampling. In addition, pathology laboratories often have biobanking infra-structure to host clinical trial tissue collections, which represents an important legacy for translational science. Funding for bio-resources is a moot point, as the activities are not without cost, but involving pathologists early in trial design will ensure these aspects are not overlooked and are adequately supported. The guidance does not define trial conduct but sets minimum standards for the documentation of cellular and molecular pathology trial protocol content. Adoption of these minimum standards will increase the transparency of clinical trials to allow results to be fully evaluated and compared, should increase the robustness of trials and improve interpretability and reproducibility.

The SPIRIT-Path guidance will have widespread applicability. Many therapeutic clinical trials, particularly in oncology, have eligibility criteria based upon a histological diagnosis. In such trials, all generated trial data and outputs, therefore, depend on the robustness of this pathological activity but no consensus guidance defining reporting of such a critical activity was previously available. Several SPIRIT-Path extensions relate to all aspects of both pathological eligibility decisions and any pathological endpoint assessment. Such assessments are important in oncological trials but also in trials of therapeutics for non-neoplastic disease, for example the critical histological assessment of disease activity in trials for the treatment of patients with ulcerative colitis³² or non-alcoholic fatty

liver disease³³. The pertinent extension items specify the documentation of the requirements for the laboratories, pathologists and translational scientists undertaking the work, including details of all stages of any specimen pathway. Protocol authors may wish to have a section of the trial protocol dedicated to pathology activities and may even consider including standard operating procedures (SOPs) within appendices.

The requirement to specify within the administrative sections the individuals responsible for the pathology content of the trial protocol will serve to allow trial protocol writers to engage with pathologists and scientists during protocol development. This should improve trial conduct using biological specimens and biomarkers and ensure that such activity within trials is appropriately recognised and resourced.

The consensus process generating the extension addressed the critical need for documentation of the requirements that relevant regulators have for evaluating different studies, for example, those using biomarkers. Without explicit documentation of the specimen and specimen pathway details that may be informed by discussion with regulators during trial design, subsequent regulatory evaluation of trial findings may be difficult and routes to approval and clinical use impossible.

The increasing use of digital images and related image analysis algorithms within pathology practice are also recognised by several extension items, both using whole-slide imaging as a tool to allow image sharing for consensus reporting and as a means of facilitating the computational evaluation of images to generate additional metrics. The application of artificial intelligence methodologies to large whole-slide image datasets may also be within the remit of the SPIRIT-AI extension⁷. The importance of both trial-specific biological specimens and histopathological images for future studies is reflected by guidance for specific documentation of explicit consent processes to allow this through increased data and specimen availability.

The study has the limitation that it necessarily involved highly motivated members of the clinical trials community that may not be fully representative. However, the generation of the first draft of

candidate items was solely based on evidence gathered by a systematic review of all published guidance, since the CONSORT Statement in 1996³⁴. This was further expanded and modified by an international group of experts within the clinical trials community representing multiple territories and stakeholder roles. The Delphi participants were chosen to more widely represent all roles within the international clinical trials community although the study was not designed to examine differences in opinion between participant groups and this cannot be formally excluded. The opportunity for a face-to-face consensus meeting requiring international travel of participants was not available due to the SARS-CoV-2 (COVID19) pandemic. However, multiple rounds of consultation in advance of an online meeting that was available for view and comment by those unable to attend virtually allowed complete consensus about the final form of the SPIRIT-Path extension to be reached.

We believe that the SPIRIT-Path extension is the necessary first step towards an approach to pathology that fully meets the needs of precision medicine. Next-generation pathology will be enabled by the application of novel biomarker tests in quality assured tissue, digitisation of morpho-molecular information, the application of computer vision technology and artificial intelligence, and integration with whole-genome analysis, including the identification of actionable mutations and assessment of tumour mutational burden.

Search strategy and selection criteria

In the prior systematic review of published guidance⁹, free-text terms such as '(histolo*; OR patholo*)' AND '(checklist; OR guideline; OR recommendation)' AND '(clinical trial; OR protocol)', along with equivalent controlled vocabulary terms, were used in the search through the databases of MEDLINE (Ovid), EMBASE (Ovid) and Cochrane Library. Additional search terms such as 'biomarker*', 'molecular diagnos*', 'practice guid*', 'study design' were also applied across the MEDLINE and EMBASE databases. Web searches on Google and Google Scholar were performed using the advanced search function, with the keywords '(Pathology; OR Histology; OR Biomarkers)'

AND '(Guideline; OR Checklist)' AND 'Clinical trial'. Only the first 3 pages (30 results) from each internet search were screened. Of the 10,184 records screened and 199 full-text articles reviewed, only 40 guidance resources met the eligibility criteria for inclusion.

Author contributions

TJK and MR had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. TJK and MR are co-chairs of the SPIRIT-Path Group. All authors had full access to all the data reported in the study and have final responsibility for the decision to submit for publication. Concept and design – All authors. Acquisition, analysis and interpretation of data – all authors. Drafting of the manuscript – TJK, MR, SJL. Revision of the manuscript – all authors.

Declaration of interests

IL is a current employee of the NCRI that supports the work of the CMPath initiative and the SPIRIT-Path Project, DJH receives administrative support for chairing CMPath. All other authors have no conflicts of interest to declare.

Data sharing

Aggregated participant responses to the Delphi survey are presented in appendix pp 3-12. Individual or attributed participant responses are not available.

Role of the funding source

The study/project funders/sponsors had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

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References

- 1 Chan A-W, Song F, Vickers A, *et al.* Increasing value and reducing waste: addressing inaccessible research. *Lancet* 2014; **383**: 257–66.
- 2 Ioannidis JPA, Greenland S, Hlatky MA, *et al.* Research: increasing value, reducing waste 2. *Lancet* 2014; **383**: 166–75.
- 3 Chan A-W, Tetzlaff JM, Altman DG, *et al.* SPIRIT 2013 Statement: Defining Standard Protocol Items for Clinical Trials. *Ann Intern Med* 2013; **158**: 200–7.
- 4 Chan A-W, Tetzlaff JM, Gøtzsche PC, *et al.* SPIRIT 2013 explanation and elaboration: guidance for protocols of clinical trials. *BMJ* 2013; **346**: e7586.
- 5 Calvert M, Kyte D, Mercieca-Bebber R, *et al.* Guidelines for Inclusion of Patient-Reported Outcomes in Clinical Trial Protocols: The SPIRIT-PRO Extension. *JAMA* 2018; **319**: 483–94.
- 6 Porcino AJ, Shamseer L, Chan A-W, *et al.* SPIRIT extension and elaboration for n-of-1 trials: SPENT 2019 checklist. *BMJ* 2020; **368**: m122.
- 7 Cruz Rivera S, Liu X, Chan A-W, Denniston AK, Calvert MJ. Guidelines for clinical trial protocols for interventions involving artificial intelligence: the SPIRIT-AI extension. *Nature Medicine* 2020; **26**: 1351–63.
- 8 Spatz A, Ruiters DJ, Busch C, Theodorovic I, Oosterhuis JW. The role of the EORTC pathologist in clinical trials: achievements and perspectives. European Organisation for Research and Treatment of Cancer. *Eur J Cancer* 2002; **38 Suppl 4**: S120-124.
- 9 Lim SJ, Gurusamy K, O'Connor D, *et al.* Recommendations for cellular and molecular pathology input into clinical trials: a systematic review and meta-aggregation. *The Journal of Pathology: Clinical Research* 2021; **7**: 191–202.
- 10 Lim SJ. The SPIRIT-Path Extension (Updated). Open Science Framework [Internet]. 2020 <https://osf.io/jeqtx>.

- 11 Humphrey-Murto S, Varpio L, Gonsalves C, Wood TJ. Using consensus group methods such as Delphi and Nominal Group in medical education research. *Medical Teacher* 2017; **39**: 14–9.
- 12 Tsihlaki A, O’Brien K, Johal A, *et al.* Development of a core outcome set for orthodontic trials using a mixed-methods approach: protocol for a multicentre study. *Trials* 2017; **18**: 366.
- 13 Nagtegaal ID, West NP, Krieken JHJ van, Quirke P. Pathology is a necessary and informative tool in oncology clinical trials. *The Journal of Pathology* 2014; **232**: 185–9.
- 14 National Cancer Institute. NCI Best Practices for Biospecimen Resources. 2016.
- 15 Rees G, Salto-Tellez M, Lee JL, *et al.* Training and accreditation standards for pathologists undertaking clinical trial work. *The Journal of Pathology: Clinical Research* 2019; **5**: 100.
- 16 Robinson M, James J, Thomas G, *et al.* Quality assurance guidance for scoring and reporting for pathologists and laboratories undertaking clinical trial work. *The Journal of Pathology: Clinical Research* 2019; **5**: 91.
- 17 Peppercorn J, Shapira I, Collyar D, *et al.* Ethics of Mandatory Research Biopsy for Correlative End Points Within Clinical Trials in Oncology. *Journal of Clinical Oncology* 2010; **28**: 2635.
- 18 Makhoulouf H, Watson MA, Lankes HA, *et al.* Toward Improving Practices for Submission of Diagnostic Tissue Blocks for National Cancer Institute Clinical Trials. *Am J Clin Pathol* 2020; **153**: 149–55.
- 19 Sarzotti-Kelsoe M, Cox J, Cleland N, *et al.* Evaluation and recommendations on good clinical laboratory practice guidelines for phase I-III clinical trials. *PLoS Med* 2009; **6**: e1000067.
- 20 LaBaer J. Improving International Research with Clinical Specimens: 5 Achievable Objectives. *J Proteome Res* 2012; **11**: 5592–601.
- 21 Hall JA, Daidone MG, Peters GJ, Harbeck N, Lacombe D, Sleijfer S. Integrating collection of biospecimens in clinical trials: the approach of the European organization for research and treatment of cancer. *Biopreserv Biobank* 2011; **9**: 181–6.
- 22 Vujančić GM, Sandstedt B, Kelsey A, Sebire NJ. Central pathology review in multicenter trials and studies. *Cancer* 2009; **115**: 1977–83.
- 23 Röcken C. Quality assurance in clinical trials—the role of pathology. *Virchows Arch* 2016; **468**: 83–92.
- 24 Orlando L, Viale G, Bria E, *et al.* Discordance in pathology report after central pathology review: Implications for breast cancer adjuvant treatment. *The Breast* 2016; **30**: 151–5.
- 25 Dancey JE, Dobbin KK, Groshen S, Jessup JM, Hruszkewycz AH, Koehler M. Guidelines for the development and incorporation of biomarker studies in early clinical trials of novel agents. *Clin Cancer Res* 2010; **16**: 1745–55.
- 26 Pell R, Oien K, Robinson M, *et al.* The use of digital pathology and image analysis in clinical trials. *The Journal of Pathology: Clinical Research* 2019; **5**: 81–90.
- 27 Mroz P, Parwani AV, Kulesza P. Central Pathology Review for Phase III Clinical Trials: The Enabling Effect of Virtual Microscopy. *Archives of Pathology & Laboratory Medicine* 2013; **137**: 492–5.

- 28 Provenzano E, Driskell OJ, O'Connor DJ, *et al.* The important role of the histopathologist in clinical trials: challenges and approaches to tackle them. *Histopathology* 2020; **76**: 942–9.
- 29 Turner NC, Kingston B, Kilburn LS, *et al.* Circulating tumour DNA analysis to direct therapy in advanced breast cancer (plasmaMATCH): a multicentre, multicohort, phase 2a, platform trial. *The Lancet Oncology* 2020; **21**: 1296–308.
- 30 Middleton G, Fletcher P, Popat S, *et al.* The National Lung Matrix Trial of personalized therapy in lung cancer. *Nature* 2020; **583**: 807–12.
- 31 Provenzano E, Bossuyt V, Viale G, *et al.* Standardization of pathologic evaluation and reporting of postneoadjuvant specimens in clinical trials of breast cancer: recommendations from an international working group. *Mod Pathol* 2015; **28**: 1185–201.
- 32 Cooney RM, Warren BF, Altman DG, Abreu MT, Travis SP. Outcome measurement in clinical trials for ulcerative colitis: towards standardisation. *Trials* 2007; **8**: 17.
- 33 Sanyal AJ, Brunt EM, Kleiner DE, *et al.* Endpoints and clinical trial design for nonalcoholic steatohepatitis. *Hepatology* 2011; **54**: 344–53.
- 34 Begg C, Cho M, Eastwood S, *et al.* Improving the quality of reporting of randomized controlled trials. The CONSORT statement. *JAMA* 1996; **276**: 637–9.

Figure 1

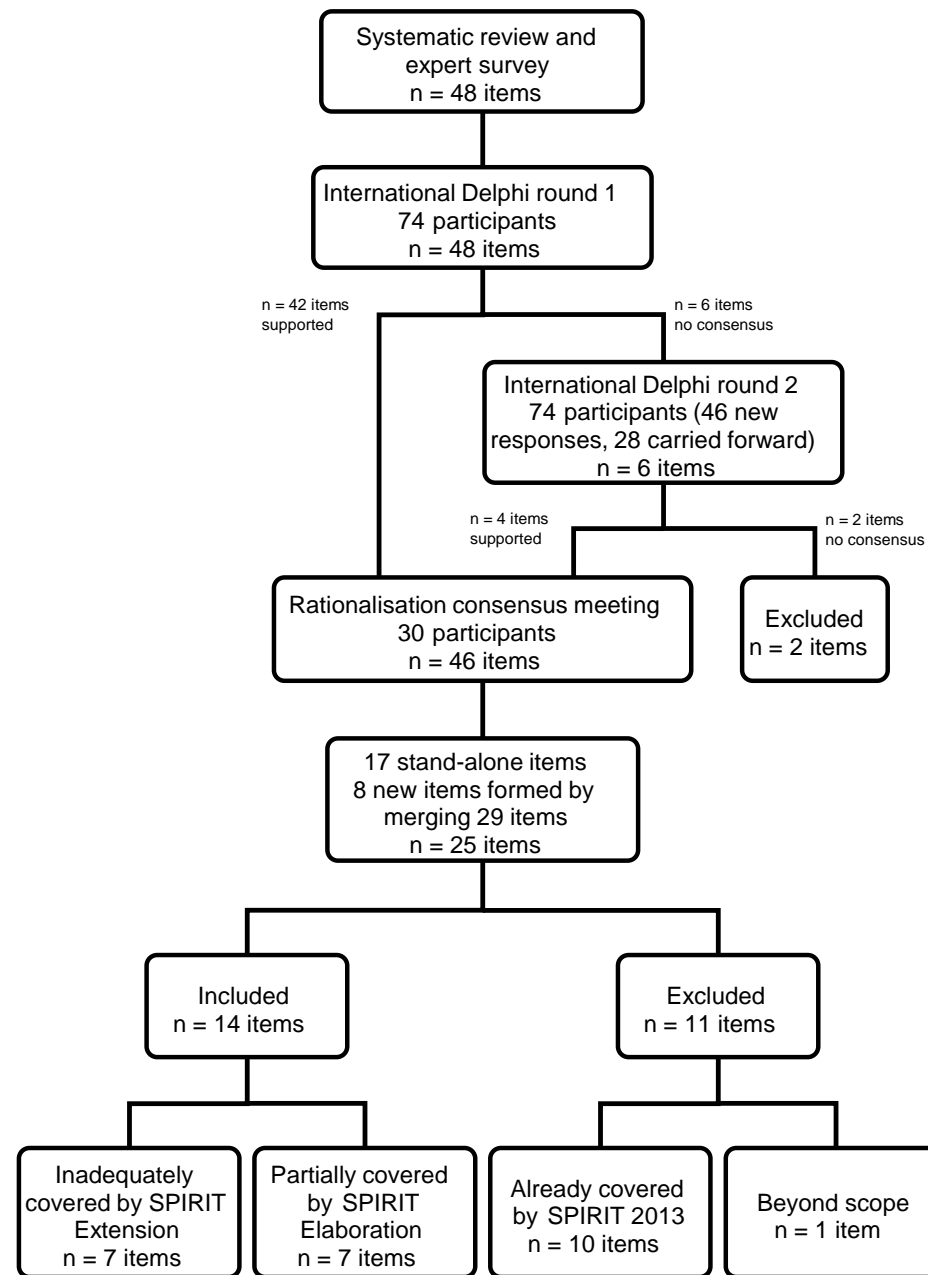


Figure 1. A flow diagram summarising the development of the SPIRIT-Path extension.

Table 1. SPIRIT 2013 and SPIRIT-Path Extension Checklist.

Domain	Item number	SPIRIT 2013 item	SPIRIT-Path item	
Administrative information				
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym		
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry		
	2b	All items from the World Health Organization Trial Registration Dataset		
Protocol version	3	Date and version identifier		
Funding	4	Sources and types of financial, material, and other support		
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	SPIRIT-Path 5a Elaboration	Specify the individual(s) responsible for pathology content of the trial protocol.
	5b	Name and contact information for the trial sponsor		
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities		

	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	SPIRIT-Path 5d Elaboration	Specify how pathology activities and roles are organised in the trial.
Introduction				
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	SPIRIT-Path 6a Elaboration	Describe the pathogenesis of the disease and rationale for any pathology-specific inclusion criteria or endpoints.
	6b	Explanation for choice of comparators		
Objectives	7	Specific objectives or hypotheses		
Trial design	8	Description of trial design including type of trial (for example, parallel group, crossover, factorial, single group), allocation ratio, and framework (for example, superiority, equivalence, noninferiority, exploratory)		
Methods: participants, interventions and outcomes				
Study setting	9	Description of study settings (for example, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	SPIRIT-Path 9 Elaboration	Describe where the laboratory work will be carried out and the accreditation status of the laboratory/site.*

Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (for example, surgeons, psychotherapists)	SPIRIT-Path 10 Extension	Where trial-specific pathology reporting is required, document specimen pathway requirements and any requirement for pathologist 'double reporting' or central review.*
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered		
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (for example, drug dose change in response to harms, participant request, or improving/worsening disease)		
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (for example, drug tablet return, laboratory tests)		
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial		

Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (for example, systolic blood pressure), analysis metric (for example, change from baseline, final value, time to event), method of aggregation (for example, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	SPIRIT-Path 12 Extension	Outline the assessment methods and the timing of tissue sampling required for any pathology-specific outcomes.*
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (Fig. 1)		
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations		
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size		
Methods: assignment of interventions (for controlled trials)				
Sequence generation	16a	Method of generating the allocation sequence (for example, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (for example, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions		

Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (for example, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned		
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions		
Blinding (masking)	17a	Who will be blinded after assignment to interventions (for example, trial participants, care providers, outcome assessors, data analysts), and how		
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial		
Methods: data collection, management and analysis				
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (for example, duplicate measurements, training of assessors) and a description of study instruments (for example, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	SPIRIT-Path 18a (i) Extension	Describe any specific accreditation, training and performance assessment requirements for trial pathologists and laboratory staff.*
			SPIRIT-Path 18a (ii) Extension	Describe the specimen documentation requirements and full specimen handling pathway.*
			SPIRIT-Path 18a (iii) Extension	Define any methods for specimen assessment by histochemical, immunohistochemical or molecular techniques.*

	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols		
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (for example, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	SPIRIT-Path 19 Extension	Describe any intended use of a digital pathology slide archive.*
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	SPIRIT-Path 20a Elaboration	Describe any methods to be used for adjusting for diagnostic drift during the trial.*
	20b	Methods for any additional analyses (for example, subgroup and adjusted analyses)		
	20c	Definition of analysis population relating to protocol non-adherence (for example, as randomized analysis), and any statistical methods to handle missing data (for example, multiple imputation)		
Methods: monitoring				

Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed		
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial		
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct		
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor		
Ethics and dissemination				
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval		
Protocol amendments	25	Plans for communicating important protocol modifications (for example, changes to eligibility criteria, outcomes, analyses) to relevant parties (for example, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)		

Consent or ascent	26a	Who will obtain informed consent or assent from potential trial participants or authorized surrogates, and how (see Item 32)		
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	SPIRIT-Path 26b Elaboration	Document enduring consent for future translational studies using tissue or any digital pathology images, if applicable.*
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial		
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site		
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators		
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation		
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (for example, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions		

	31b	Authorship eligibility guidelines and any intended use of professional writers		
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	SPIRIT-Path 31c Extension	Describe the mechanism and timing for making digital pathology images available, if applicable.*
Appendices				
Informed consent materials	32	Model consent form and other related documentation given to participants and authorized surrogates		
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable.	SPIRIT-Path 33 Elaboration	Specify the regulatory approvals required for clinical trial samples to be used in future work.*

** Applies to clinical trials where there is a requirement for trial-specific specimen activity outside of the routine diagnostic pathway, including acquisition of trial-specific samples or review/analysis of historical samples.*

Thank you for your further comments and interest in our manuscript. We have addressed these as documented in our response to each point.

Editorial comments:

1. Table: apologies, but although a reviewer suggested this, please could you remove the additional column re: protocol page(s) from the table, as it would just be a blank column in the table and doesn't therefore really fit with Lancet house style.

No problem. We have removed this column from the table.

2. Please provide a title and legend for the figure. Figure legends should be a maximum of 30 words.

We have provided a figure legend in the .pptx file.

3. Please move the specific details of your literature search into a separate panel entitled 'Search strategy and selection criteria', as per Lancet house style. I suggest that the text starting with "Free-text terms such as '(histolo*; OR patholo*)'..." through to "...only 40 guidance resources met the eligibility criteria for inclusion" could be moved out of the main Methods into this separate panel.

We have moved this text into a separate panel, as advised, placed after the Discussion based on the layout of a recently published systematic review in *The Lancet Oncology*.



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