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TranspariMED input to NIHR consultation on its proposed guidelines to boost trial registration and timely disclosure of results

TranspariMED works to end evidence distortion in medicine. TranspariMED strongly welcomes NIHR's consultation on NIHR guidelines to boost trial registration and timely disclosure of results. NIHR has long been a global front-runner in clinical trial transparency, to the benefit of UK taxpayers and patients in the UK and beyond.

The proposed "NIHR policy on prospective trial registration and timely disclosure of Clinical Trial results" is strong overall and another significant step forward, while also being laudably brief and clear. However, in some places it still falls short of WHO Joint Statement commitments, the global best practices in clinical trial transparency identified by Transparency International and Cochrane, and universal transparency criteria. Hence, it could be further improved.

Please note that in August 2018, Transparency International, Cochrane and TranspariMED wrote a joint letter to NIHR urging it to "fully implement" the provisions of the WHO Joint Statement. See this checklist.

Potential areas for improvement are discussed below.

Point 2.1 [Scope]: All Clinical Trials in receipt of Research Costs from NIHR.

Comment:

Under both EU regulations and US legislation (FDAAA), it is trial sponsors and not principal investigators that are responsible for posting summary results. However, trial registration – as per Declaration of Helsinki – is commonly regarded as the responsibility of the individual researcher. This can cause confusion, impede compliance, and undermine accountability.

At UK universities, registry management and summary results posting is increasingly being centrally performed by Research Governance teams rather than by individual researchers. This is a positive development that seems likely to increase the quality of registry entries, and should be welcomed, but it shifts key roles and responsibilities from individuals to institutions.

At the same time, many researchers and even some research governance staff currently seem to have a very limited understanding of the most basic registry requirements and best practices, including who is ultimately responsible for doing what.

Recommendations:

- NIHR's policy should clearly state who exactly is ultimately responsible – and will be held accountable by NIHR – for compliance with its policy, in particular the elements relating to (a) registering trials, (b) keeping trial registries updated, and (c) posting summary results onto registries.

- In the medium term, NIHR should consider requiring UK research institutions to themselves adopt policies and processes that fully conform to the provisions of the WHO Joint Statement as a precondition for being eligible to host research projects funded by NIHR.

Point 3.1: All NIHR-funded primary research projects are required to register onto ISRCTN…

Comment:

WHO recommends that trials should be registered on as few WHO primary registries as possible, i.e. ideally on just one registry. Single registration not only makes life easier for registry users such as systematic reviews, it also - and possibly more importantly - reduces the administrative burden placed on trial sponsors and registry managers. In the case of trials that, due to regulatory requirements beyond NIHR's control, also have to register on EUCTR and/or Clinicaltrials.gov, this requirement inevitably creates multiple registry entries for the same trial.

Recommendation:

- NIHR should consider waiving the ISRCTN registration requirement for CTIMPs and/or for trials required to register on CT.gov under US law, and ensure that each trial is registered on one WHO primary registry only.

Point 4: Registries should be updated during the study and key outcomes and trial protocol are to be made publicly available within 12 months of study completion

Comment:

The inclusion of a requirement to post summary results within 12 months of a trial's primary completion point (rather than overall study completion) is a core element of the WHO Joint Statement, and NIHR's integration of this requirement into its policies is essential to achieve full compliance.

Recommendation:

- Require summary results to be posted onto a registry within 12 months of a trial's primary completion point. Adopt the same time frame for protocol publication, and – as per the WHO Joint Statement – add that the protocol should include amendments.

Point 4.3: Summary Results should be quality assured and validated by the research team however NIHR acknowledge this may mean the results have not been Peer Reviewed and therefore should not be used to inform practice.

Comment:

NIHR's trial registry of choice, ISRCTN, is unusual among major trial registries in that it currently does not support the posting of summary results as a standard function. While it may be possible to 'quick fix' this by allowing users to upload key results in some form, e.g. as a PDF, this would fall significantly short of the standards of other trial registries. Both Clinicaltrials.gov and EUCTR have clear formats and processes for summary results to ensure that data is adequately reported against the pre-defined outcomes, and their staff proactively engage with researchers and review the data provided to ensure that these standards are met. A 'quick fix' of ISRCTN could endanger the quality and utility of outcome reporting on a key registry, and thereby undermine evidence-based medicine more broadly.

Recommendations:

- NIHR should work with ISRCTN to set up a summary results posting function that meets or exceeds those already used by Clincialtrials.gov and EUCTR in terms of data quality assurance, user utility, public visibility of late or incomplete reporting, machine readability and – crucially – user friendliness. If ISRCTN itself is unable to perform quality assurance (or outsource this function), NIHR should consider setting up an internal quality assurance function for summary results uploaded onto ISRCTN by NIHR grantees.

- The beta version of this function should be pre-tested with UK university staff already familiar with uploading summary results onto multiple registries, and adjusted in line with their feedback. Both EBM Data Lab in Oxford and the US-based Clinical Trials Registration and Results Reporting Taskforce have considerable relevant expertise and could be closely consulted throughout the design and development process.

Point 5.1: Publication of trial findings in a Peer Reviewed open access journal is also an expectation. NIHR acknowledge publication in a Peer Reviewed journal is not within the complete control of the research team and so set an indicative timeframe of 24 months from Primary Study Completion.

Comment:

An 'expectation' is not a requirement. Furthermore, journals are currently riddled with trial reports that do not meet basic quality and integrity standards. The very limited impact of past reform efforts indicates that this is extremely unlikely to change significantly in the foreseeable future.

Recommendations:

- A clear publication deadline for journal-based results sharing could incentivize both researchers and journals to accelerate the publication process. As journal publication timelines are beyond the control of research teams, NIHR should consider requiring researchers to pre-publish their results in academic journals allowing this publication form if conventional journal publication has not been achieved within 24 months.

- **NIHR should include a brief sentence stating that it regards 'silent' outcome switching as research misconduct**, and that authors silently adding or suppressing outcomes in journal

publications will be ineligible for future grants. While NIHR cannot be expected to comprehensively monitor compliance, it could consider annually reviewing a small random sample of publications for outcome switching as a deterrent.

- In the long term, NIHR should aim at requiring all journal publications to follow the Registered Reports model. This would not only improve trial design quality and reduce publication bias, but could potentially also substantially accelerate post-trial-completion publication timelines. As the journal infrastructure to enable this does not yet exist in the field of clinical trials, NIHR should begin actively engaging journal editors in a dialogue on this topic as soon as possible.

Point 6.2: Applicants may alternatively comment on why prospective registration and/or publication was not possible.

Comment:

Failure to register and/or report trials is an ethics violation under the Declaration of Helsinki. Extending public funding to unethical researchers to conduct new trials involving human participants on the sole condition that they 'comment' on their past unethical behaviour is ethically highly questionable.

In addition, this policy element falls short of WHO Joint Declaration accountability standards: "Reporting of previous trials realises the value of funding; therefore the contribution made from reporting previous trials, whatever their results, will be considered in the assessment of a funding proposal." [emphasis added]

Furthermore, it is unlikely that requiring applicants to merely 'comment' would be sufficient to incentivize the retrospective registration and/or publication of missing trial results, or to act as a deterrent to future non-registration or non-reporting of trials supported by funders other than NIHR.

Recommendations:

- **NIHR should leverage this mechanism to promote the retrospective registration and/or posting of summary results onto registries by applicants.** Specifically, applicants should be required to retrospectively register and/or post results for all past trials that breached ethical norms, as a condition of receiving a new grant. Applicants who fail to clear their backlog of unregistered and/or unreported trials by the time the new grant closes out should be made ineligible to receive future funding from NIHR. This would integrate the "considered in the assessment" element noted above into NIHR policy.

- NIHR should consider providing additional funds to enable this, balancing this against the danger of moral hazard. Note that this measure would be a highly cost-effective use of public funds, as it would put the results of many older trials onto the public record at marginal cost.

- NIHR should actively audit compliance and make public the names of researchers who failed to meet their ethical and contractual obligations. Compliance audits should include data completeness checks on registries to prevent researchers from 'gaming the system' by making sub-standard entries on registries.

- Excellence in results reporting is an integral part of overall research excellence. Researchers based at institutions with a weak institutional track record of summary results posting onto registries pose an elevated policy compliance and fiduciary (research waste) risk to NIHR, not

least because registry maintenance is often institutionally managed (see above). NIHR grant proposal scoring templates should be adjusted to include EUCTR trials tracker (and possibly FDAAA trials tracker) scores to ensure that institutional results posting performance will be "considered in the assessment" of grant proposals. NIHR should adopt and communicate this policy now, but grant a grace period of two years to give institutions sufficient time to clear their backlogs of unreported trials that violate EU guidelines (and possibly US transparency laws).

Point 7.1: Clinical Trial registry records should be updated as necessary to include final enrolment numbers achieved, and the date of Primary Study Completion (defined as the last data collection time point for the last subject for the Primary Outcome measure).

Comment:

The updating requirement is salient and highly welcome. However, it omits one WHO Joint Statement element, and some jurisdictions and trial registries have updating requirements that go beyond these two items. This could cause confusion and non-compliance with registry requirements.

Recommendations:

- According to the WHO Joint Statement, policies should include the requirement that registry entries are updated if a trial is terminated, including disclosure of n recruited. NIHR should add this element to its policy.

- NIHR should review existing Clinicaltrials.gov, EUCTR and ISRCTN registry requirements regarding updates, and ensure that its updating requirements are broadly aligned with them, while being kept as brief, simple and comprehensible as possible. A separate plain language information sheet / appendix summarizing Clinicaltrials.gov, EUCTR and ISRCTN registry requirements regarding updates could improve compliance.

Point 7.3: When in place, NIHR will make summary reports on compliance available in the public domain

Comment:

NIHR should not re-aggregate granular data it holds to shield unethical medical researchers and institutions with weak research integrity safeguards from public view.

The WHO Joint Statement explicitly states that "We agree that transparency is important and therefore the outputs from the monitoring process will be publicly available". 'Summary reports' constitute only a small part of overall "monitoring outputs", and fall short of universal transparency and accountability standards commonly applied in democratic societies.

For example, if a public body in the UK only published summary reports of human rights violations within prisons, without disclosing which prisons these violations took place in and who was managing each prison, this would be considered non-transparent.

Recommendations:

- **Setting up a monitoring system was a commitment NIHR made over a year ago when it signed up to the WHO Joint Statement. It is disappointing that no such system has yet been put into place.** NIHR should publicly, though a press release or public statement, set a target

date by which it will have put into place a "system to monitor results reporting on an ongoing basis" [WHO Joint Declaration, emphasis added] and started publishing quarterly narrative audit reports and the accompanying data sets.

- **Monitoring data should be published in non-aggregated, line by line format**, including but not limited to the following data: research grant number, clinical trial (registry ID) number, trial primary completion date, amount of funding received from NIHR, name of principal investigator, name of the institution at which the principal investigator was based when conducting the trial, name of trial sponsor as noted in registry, and the email address of the party responsible for posting results.

- In addition to being a transparency imperative, making this data public in line by line format would help research institutions to detect and address gaps in their current internal policies and process, and could increase compliance rates by allowing third parties to independently follow up on unregistered and/or unreported trials. See also TranspariMED's most recent submission of evidence to the Commons Science and Technology Committee on this issue. Note that HealthWatch UK, Universities Allied for Essential Medicines UK and STOPAIDS have endorsed the principle of line by line publication of trial audit results.

- Some players in medical research sector still regard the release of detailed performance data as 'naming and shaming', even though this has long been routine in other sectors. However, the publication of granular data also creates positive incentives by giving credit and public visibility to researchers and institutions who excel.

- Once the NIHR monitoring system has been set up, NIHR should convene other WHO Joint Statement signatories for a study tour. This would deliver on the WHO Joint Statement commitment that "We agree to share challenges and progress in the monitoring of these policies".

Definitions:

Comment:

NIHR's definition of 'clinical trial' differs from that used by the WHO. The latter forms the basis of the WHO Joint Statement and hence form the foundation of global best practices.

Recommendation:

- NIHR should adopt the WHO definition of 'clinical trial': "[A] clinical trial is any research study that prospectively assigns human participants or groups of humans to one or more health-related interventions to evaluate the effects on health outcomes. Interventions include but are not restricted to drugs, cells and other biological products, surgical procedures, radiological procedures, devices, behavioural treatments, process-of-care changes, preventive care, etc."

- NIHR should actively encourage the adoption of the WHO definition across the UK research landscape to promote the harmonization of policies around WHO best practices.

Additional comment:

The UK research landscape currently lacks the equivalent of the US-based Clinical Trials Registration and Results Reporting Taskforce, an excellent initiative whose membership is currently not open to

non-US institutions. NIHR could help to provide an important public good by catalysing the setup of a similar Taskforce in the UK, with non-profit institutions worldwide eligible for membership. Note that the US Taskforce is run on a tiny budget; the UK equivalent could eventually be financed through membership contributions and/or small grants, so this would be a highly cost-effective seeding investment.

Please note that ISRCTN, EBM Data Lab and the Clinical Trials Registration and Results Reporting Taskforce did not review or provide input into this document.

[ENDS]