

Please see below for a link to the webinar recording for the Trials Methodology Research Partnership:

Using site and trial experience to ensure the quality of eligibility criteria

Will Cragg (University of Leeds)

08 July 2021

On behalf of the UK Trial Managers' Network

The slides are also available below.

For any queries, please contact uktmn@nottingham.ac.uk

<https://www.youtube.com/watch?v=jdzJMK3IB3g>

Using site and trial team experiences to ensure quality of trial eligibility criteria

**Trials Methodology Research Partnership /
UK Trial Managers' Network**

**Will Cragg, Clinical Trials Research Unit,
University of Leeds**

8 July 2021



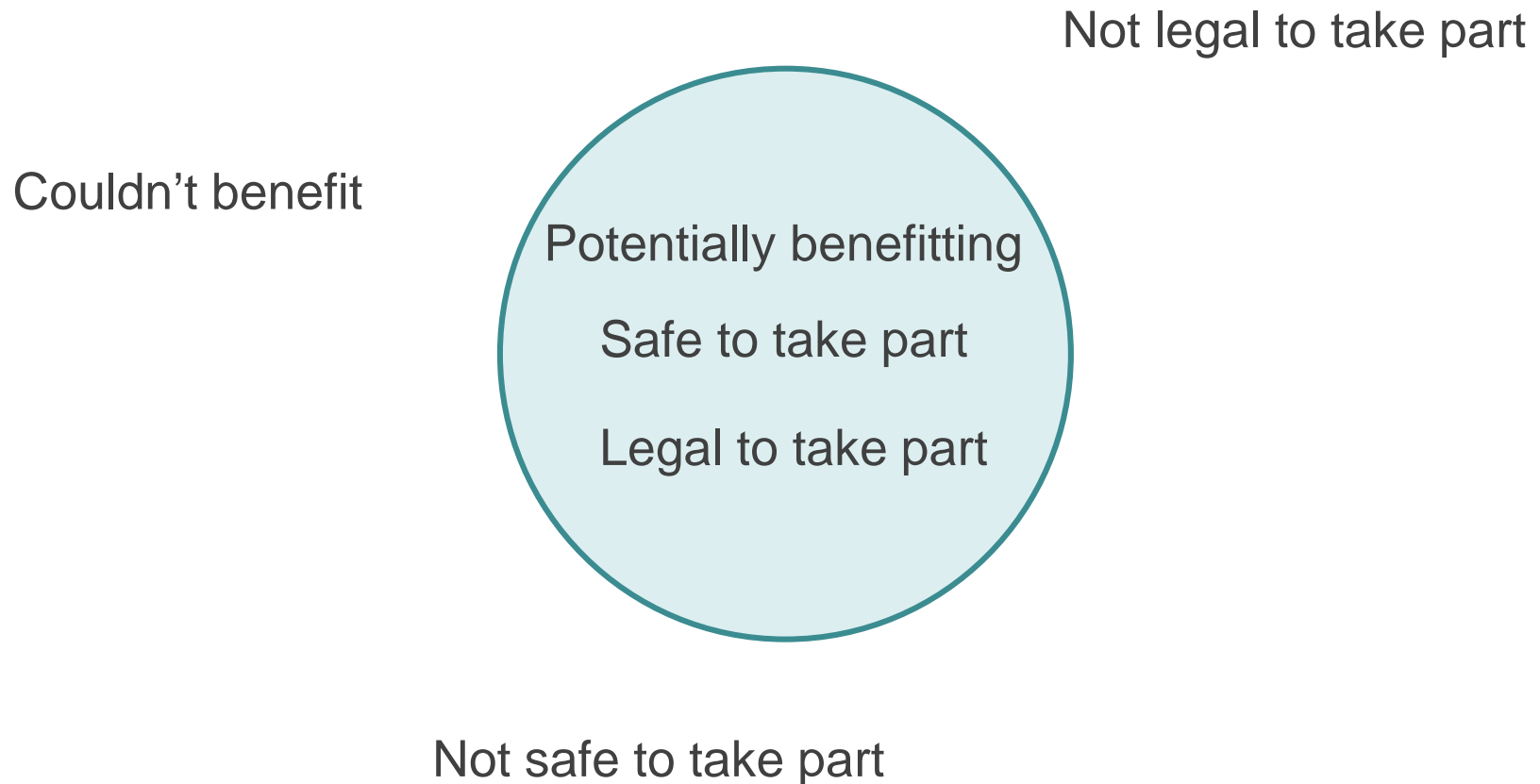
Using site and trial team experiences to ensure quality of trial eligibility criteria

- Introduction
- Learning from past issues
- Standardising elements of eligibility criteria
- Quality control process
- Recruiter survey
- Concurrent literature review
- Conclusions & suggestions

Eligibility criteria – fundamental trial design element



Eligibility criteria – fundamental trial design element



What should eligibility criteria look like?

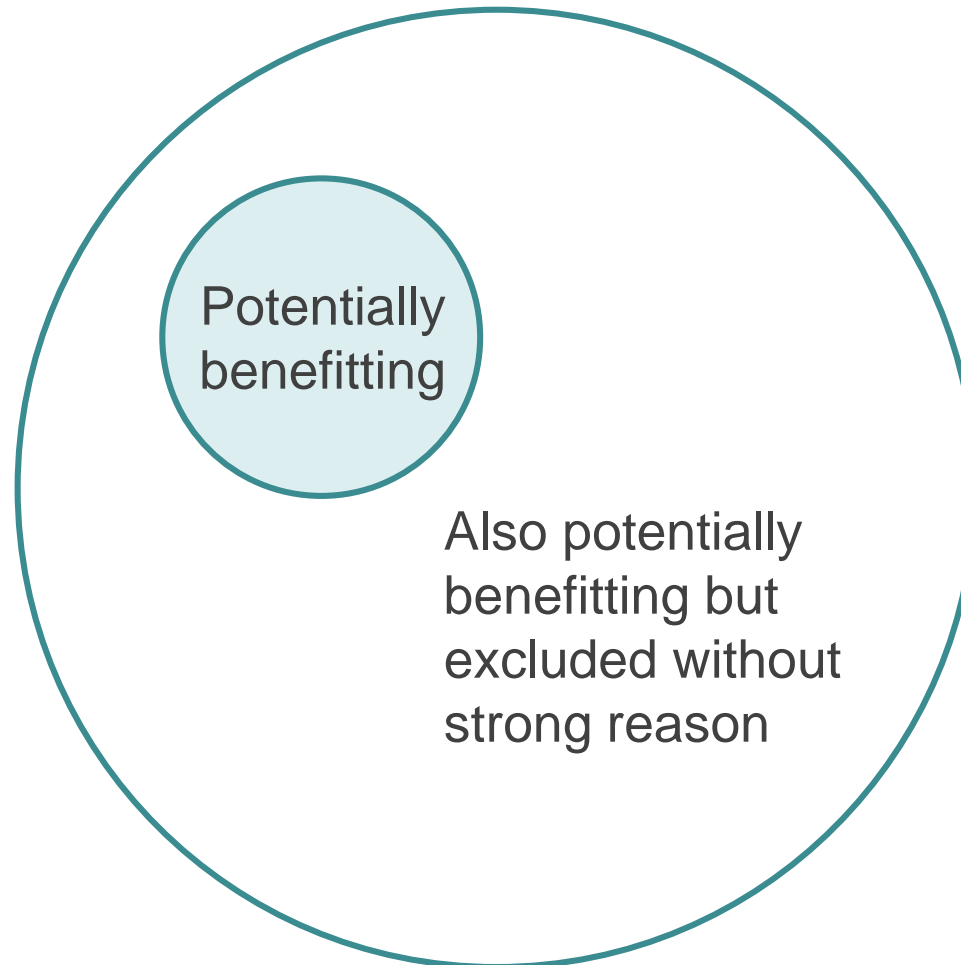
- ICH Good Clinical Practice guideline: trial protocol should include “subject inclusion criteria” and “subject exclusion criteria”
- SPIRIT statement: “inclusion and exclusion criteria”
 - Emphasizes “clear delineation”
 - Need to consider generalisability (“When trial participants differ substantially from the overall population to whom the intervention will be applied, the trial results may not reflect the impact in real world...settings”)
- HRA CTIMP protocol template:
 - “precise definitions”...
 - “should be clear so they can be applied consistently”...
 - “definitions for the timelines and flexibility of each...criterion must be carefully considered”
- **No set standards e.g. format, standard elements – surprising?**

What should eligibility criteria look like?

- Perhaps:
 - *Well chosen*
 - *Well written or communicated*
 - *Well applied?*

What if they are not well chosen/written/applied?


- #1: criteria too narrow, affecting recruitment, generalisability; denying access to research benefits



What if they are not well chosen/written/applied?

- #2: criteria do not protect patients

Not safe to
take part

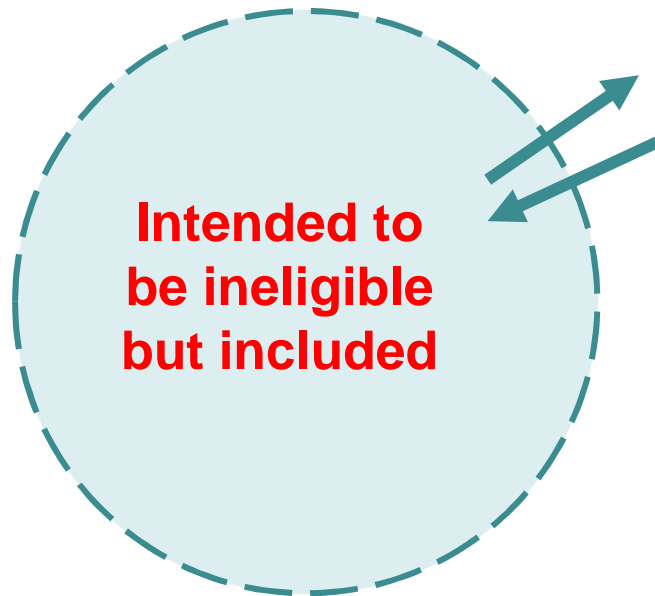


Not safe to
take part

What if they are not well chosen/written/applied?

- #3: criteria written or applied incorrectly -> classification errors

**Intended
to be
eligible but
excluded**



Reporting is also important

- Trial registration (SPIRIT / registry requirements)
- Trial results (CONSORT)
- Some reported issues with clarity and consistency of reporting, e.g. unexplained differences between registry and final results
 - Gandhi *et al.* Eligibility criteria for HIV clinical trials and generalizability of results: The gap between published reports and study protocols. *AIDS*. 2005;19(16):1885-1896
 - Blümle *et al.* Reporting of eligibility criteria of randomised trials: Cohort study comparing trial protocols with subsequent articles. *BMJ*. 2011;342(7805).

Do things sometimes go wrong?

- Reporting on this also limited!
 - Only ~ 38% trial reports found to report information about eligibility errors
 - Yelland *et al.* Prevalence and reporting of recruitment, randomisation and treatment errors in clinical trials: A systematic review. Clin Trials. 2018
 - Sweetman *et al.* Failure to report protocol violations in clinical trials: a threat to internal validity? Trials. 2011;12:214. doi:10.1186/1745-6215-12-214
 - Errors may occur in ~1% of patients – with some higher outliers (e.g. up to 20%)
 - See references on additional slide
- **Is it a big problem?**

Motivation for our work

- Specific issue in a trial in our CTU:
 - Exclusion criterion around medical history
 - Associated medical test to check within 14 days of randomisation, but elsewhere in protocol
 - Some sites missed the link, thought they could rely on prior testing
 - Mitigated by prior testing and other routine tests – so no significant safety issues raised in this case
- QA involved to review and consider corrective/preventative actions
 - Fundamentally a communication issue?
 - **Can we avoid this sort of issue through improving how we write our criteria or design our protocols?**
 - **What else can we do to make sure our eligibility criteria are fit for purpose?**

What we did #1: learning from past issues

- Reviewed cases of eligibility criteria not quite working as planned
- 14 criteria reviewed from across current/previous trials
- Issues included:
 - Ambiguous/potentially confusing wording
 - Issues with clarity or feasibility of eligibility tests or timelines
 - Uncertainty about timeframes for past medical history tests
 - Wording which, when correctly applied, excluded more patients than intended (no waivers allowed...)

What we did #2: standardising elements

- Discussed prior issues, devised 'formula' for eligibility criteria

Clear statement allowing binary response

+

Timeframe of condition (if not implied)

+

Method of assessment

+

Timeline of assessment

Inclusion: Diagnosed with [condition]

+

[Timeframe implied: occurred in the past and still requiring treatment/care]

+

Assessed by: diagnostic test

+

Within the last 4 weeks (i.e. requiring first-line treatment), or any time in the past

Clear statement allowing binary response

+

Timeframe of condition (if not implied)

+

Method of assessment

+

Timeline of assessment

Inclusion:
Adequate renal function, based on creatinine clearance

+

[Timeframe implied: currently]

+

Assessed by:
blood test, with CC calculated according to Cockcroft-Gault or other locally approved formula

+

Within 14 days of randomisation

Inclusion:
Well enough to receive treatment

+

[Timeframe implied: currently]

+

Assessed by:
opinion of the responsible clinician

+

Within 14 days of randomisation

Clear statement allowing binary response

+

Timeframe of condition (if not implied)

+

Method of assessment

+

Timeline of assessment

Exclusion:
Received certain prior therapy

+

Timeframe:
within the last 6 months

+

Assessed by:
reviewing medical records

+

At the time of
assessing eligibility

Exclusion:
Pregnant or breastfeeding

+

[Timeframe implied: currently]

+

Assessed by:
pregnancy test, asking patient

+

Within test within 7 days of randomisation

Exclusion:
Known history of certain heart problems

+

[Timeframe implied: at any time or specified time limit]

+

Assessed by:
reviewing medical records

+

At the time of
assessing eligibility



What we did #3: quality control process

- **Can a structured review process improve quality?**
- Devised staged review process for drafted eligibility criteria
- Tried out in several trials
- Process:
 - **Trial Manager** reviews for completeness
 - **Chief Investigator** reviews for correct scope, and for any required caveats (i.e. would the criteria include and exclude the right people?)
 - **Peer reviewer** (internal) reviews for clarity
 - **Site staff** review for clarity and feasibility
 - **Data manager** reviews to consider data collection and central monitoring aspects

What we did #3: quality control process

- Some positive feedback, particularly from the trial manager review
 - process was a useful reminder to check specifics of eligibility criteria
- However...
 - Not always easy to get others to engage with the review process
 - Best timing not obvious
 - Can the reviews/reviewers actually influence the protocol?
 - Might training / templates be better? (Further 'upstream' in the process)

Suggestions on 'clarity'

- **Subjective, however suggestions in the QC process include:**
 - Focus each criterion on one thing, not several
 - Avoid non-specific or subjective language like 'ongoing use of X' or 'presence of established X'
 - Don't base criterion on future events
 - ('patient must not do X for duration of the trial', but rather 'patient has agreed not to do X')
 - Refer to the thing you want to exclude, not a result of it
 - (e.g. imagine you want to exclude people taking treatment Y; don't say "must not have X requiring Y", as there may be other situations where Y is used; instead, simply say "must not be taking Y")

Suggestions on 'clarity'

- **Subjective, however suggestions in the QC process include:**
 - Specify where more than one of something may exist; e.g. don't just say "performance status 0 or 1", but specify the performance status model to be used
 - Avoid use of / where the intended meaning is actually "and"



What we did #4: recruiter survey

- Decided to ask for recruiter feedback – directly from collaborators on our trials and indirectly through NIHR contacts lists and social media
- Deliberately short survey – prioritizing number of responses over depth of responses
- Eligibility for survey: use of eligibility criteria to assess potential trial participants



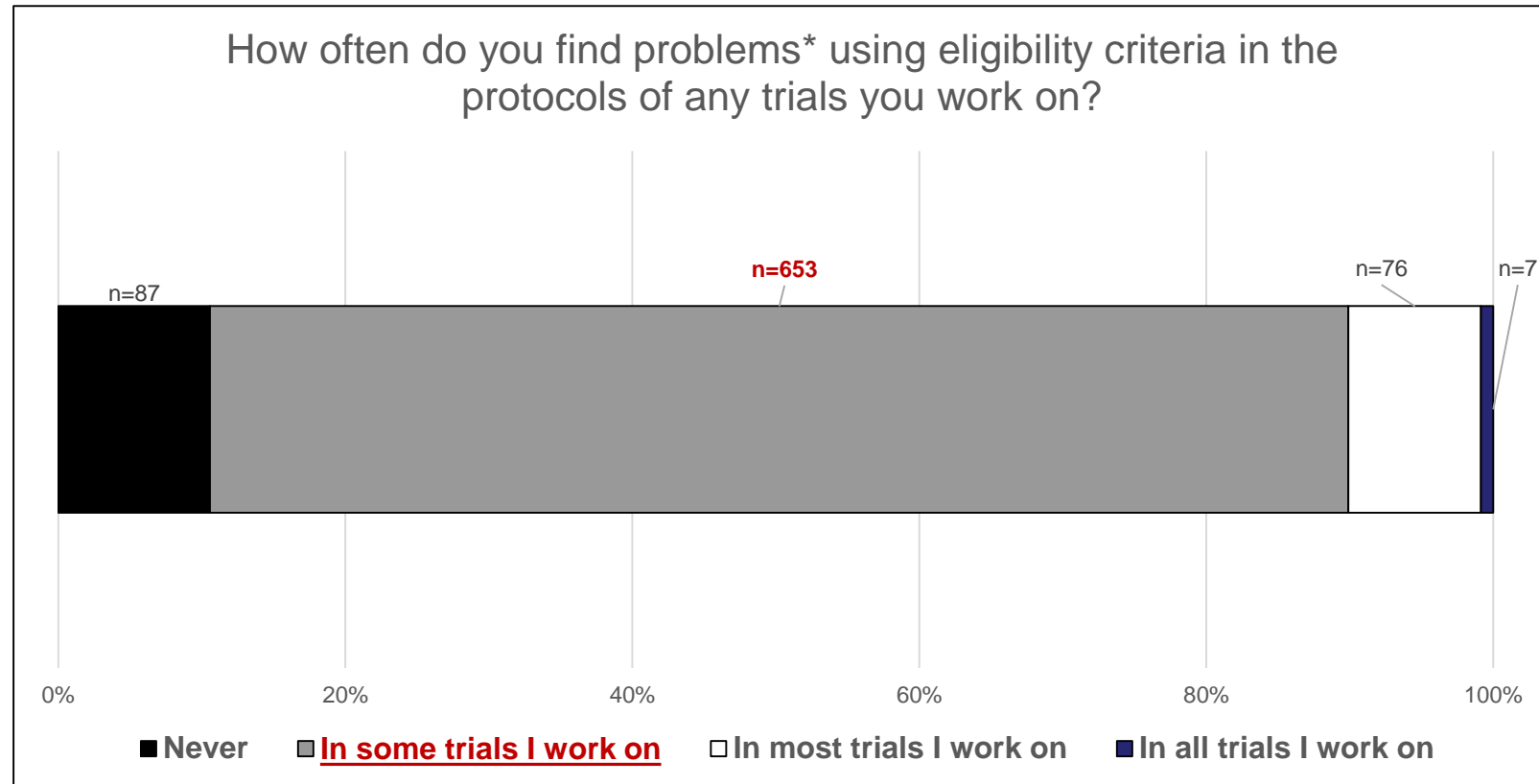
What we did #4: recruiter survey

- Aimed to find out:
 - Do they experience problems with using eligibility criteria?
 - If so, how often and what sort of problems?
 - How do they access eligibility criteria information when they need it?
 - Would they be interested in reviewing eligibility criteria as part of the protocol development process?
- Small number of 'demographics' questions – anonymous responses
- Experiences from any trials, not just ours

What we did #4: recruiter survey results (1)

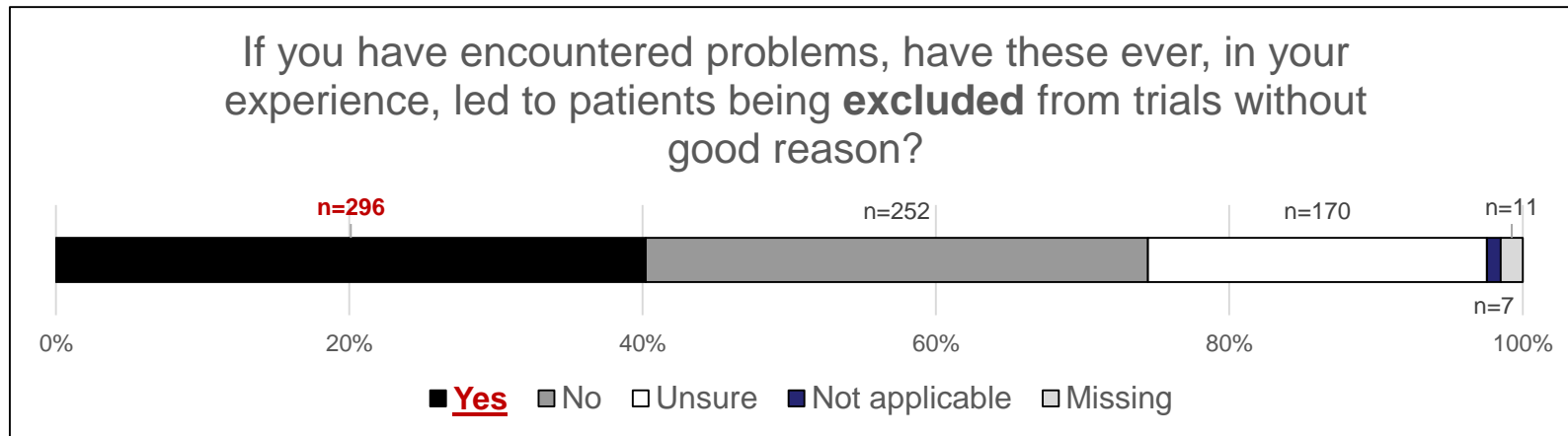
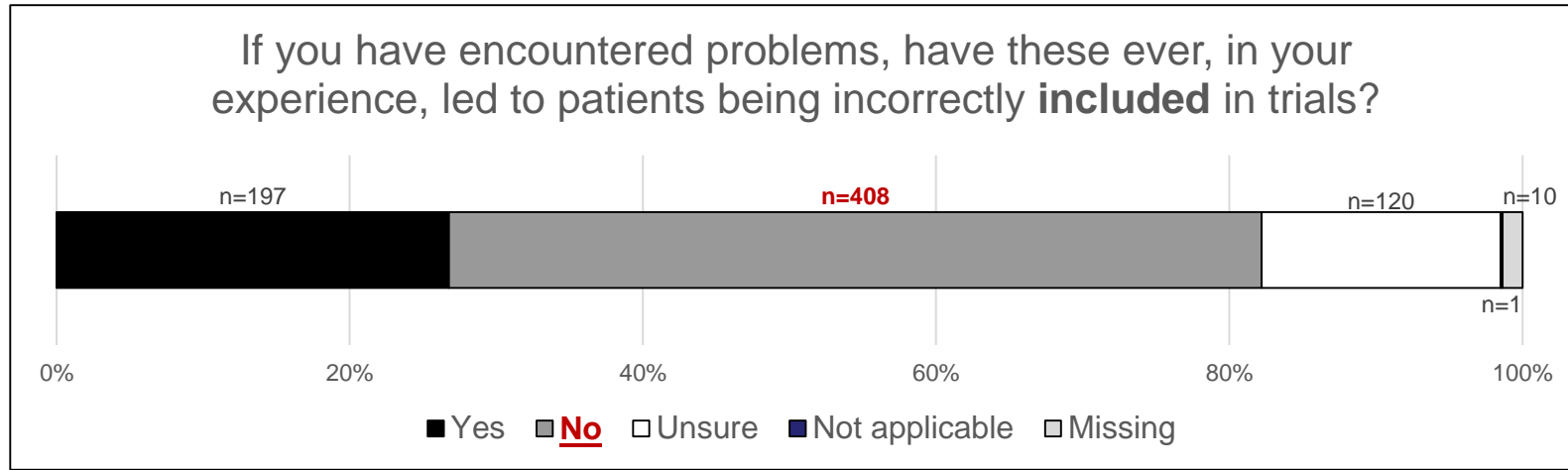
- Survey open in August-September 2019
- 823 eligible responses (874 in total)
- Mainly: not medical doctor, experienced in secondary care, no experience writing eligibility criteria, experience with both CTIMPs and non-CTIMPs
- Amount of experience with trials varied but largest group >10y experience (~35%)

What we did #4: recruiter survey results (2)



* (For example, unclear or ambiguous wording, mandated tests which are not easy for you to do within the given timeline, or other problems)

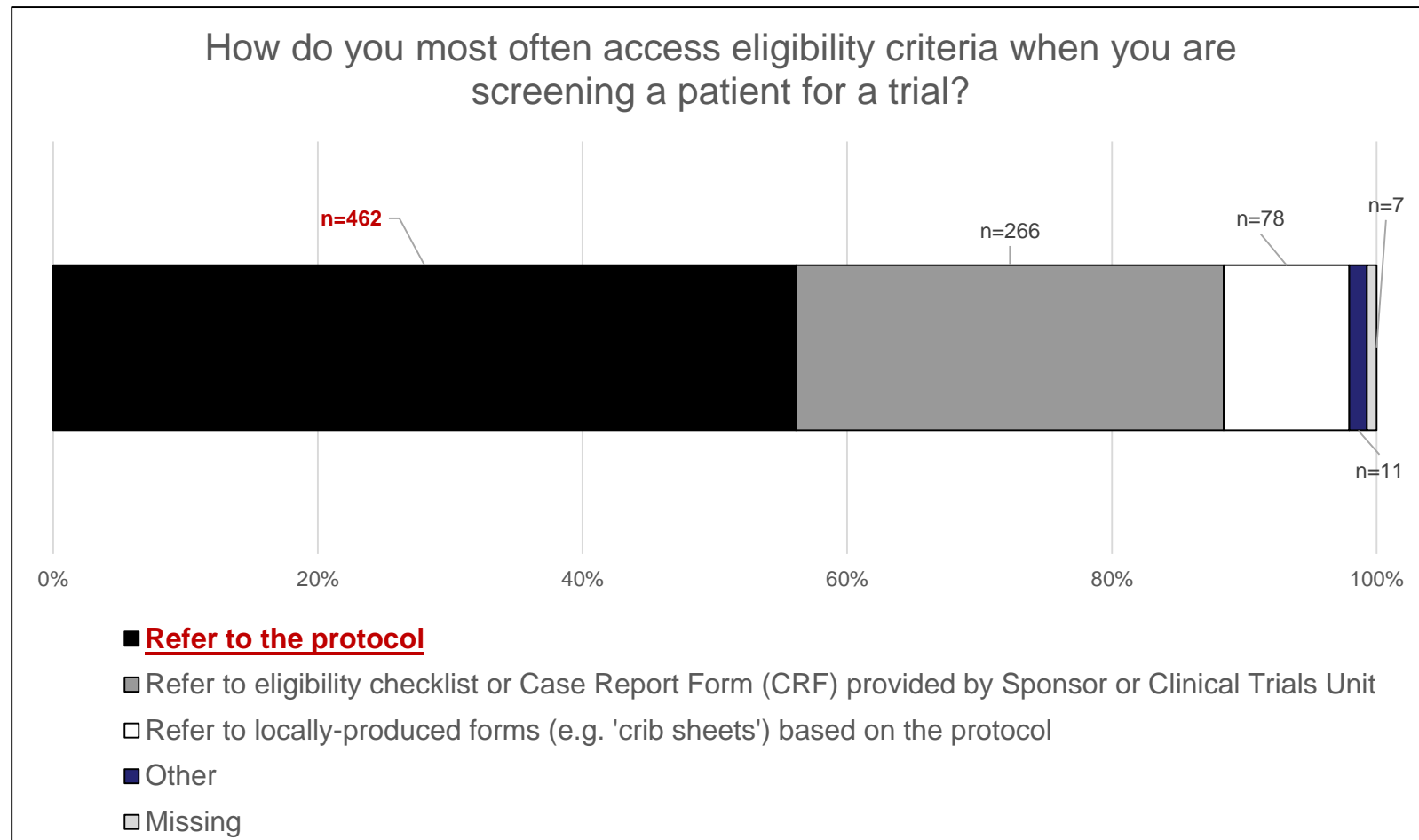
What we did #4: recruiter survey results (3)



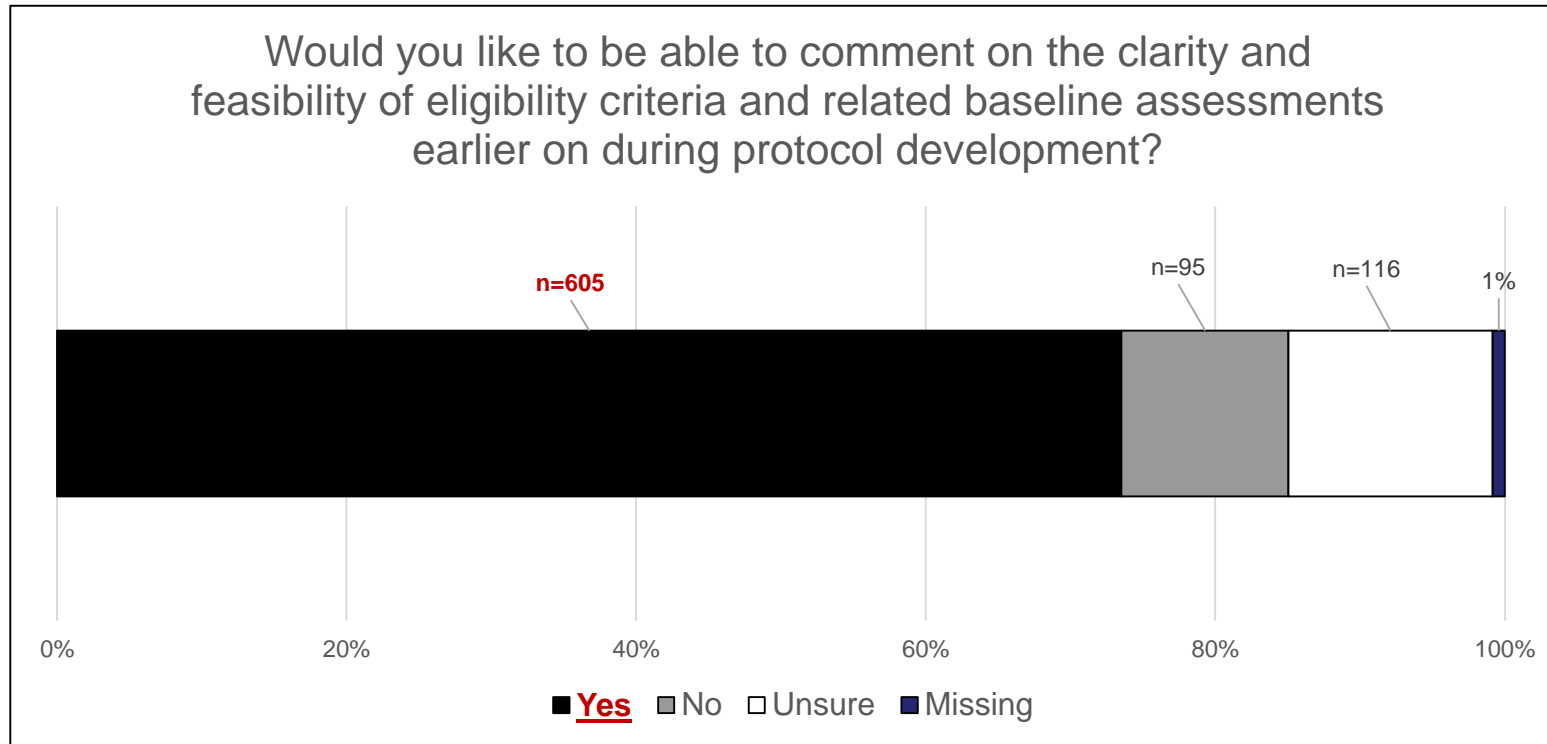
What we did #4: recruiter survey results (4)

- Analysis of free-text responses about sorts of problems experienced:
 - 67% mentioned clarity (meaning of eligibility criteria unclear)
 - 34% mentioned feasibility (meaning clear, but hard to achieve in practice)
 - 14% mentioned suitability (meaning clear and feasible, but disagree that criteria are necessary)
- Respondents **without** CTIMP experience more likely to say **never** experienced problems (29% vs 9% in those with CTIMP experience)

What we did #4: recruiter survey results (5)



What we did #4: recruiter survey results (6)



What we did #4: recruiter survey - conclusions

- Corroborates previous reports that problems sometimes occur in using eligibility criteria (more so in IMP trials?)
- Recruiters most commonly report issues with clarity, but also mentioned feasibility and suitability
- Recruiters report more frequent incorrect exclusions than inclusions
 - Links to wider, recognised issues with generalisability
 - Risk-aversion – more effort to prevent incorrect inclusions?
 - Short-termism?
- Useful to know how recruiters access criteria (protocol or CRF)
- Some limitations – e.g. information depth, question validation, self-selecting respondents

What we did #4: recruiter survey - conclusions

- Significant support for being involved in reviewing draft criteria – but how to do it?
 - Would they really be able to influence protocol?
 - Time added to setup?
 - What if different sites disagree?



What we did #5: literature review

- Concurrent & not systematic – used keywords and reference/citation searching
- Looking for best practice in designing/implementing eligibility criteria
- Significant work preparing eligibility criteria for ‘automation’ or computer-readability, for tasks e.g. searching electronic health records
- Lots about generalisability (problem, potential solutions)
- More about *choosing* than *writing*
- Not much from *quality* perspective

What we did #5: literature review

- Suggested quality improvement methods
 - “Expert case review”
 - (Vining *et al*, “eligibility determination for clinical trials...”)
 - (Spragg *et al*, “an informatics strategy to assure enrollment criteria compliance...”)
 - Run-in periods
 - (Simpson *et al*, “A systematic review of techniques and interventions for improving adherence to inclusion and exclusion criteria...”)
 - Audit-feedback process
 - (Roos *et al*, “Eligibility audits for the randomized neuropathic bone pain trial...”)
- No robust data, and scalability/generalisability uncertain
- Justified effort in all trials?

Conclusions & suggested way forward (1)

- Problems arise routinely in relation to trial eligibility criteria, and we should do what we can to reduce their frequency
- Computer-readable criteria may become more important and resolve some problems, but humans will still need to read them for a while yet
- Generating robust evidence about eligibility criteria design may not be straightforward
- Might be possible/advisable to agree standard elements for all criteria
- Building required elements into training and design rather than a QC process may work best
- Further work needed to demonstrate benefit of our suggestions
- There is substantial recruiter interest in the topic
- Recruiters confirmed issues with clarity and feasibility, also highlighted suitability of criteria

Conclusions & suggested way forward (2)

- Some practical things we can do now:
 - Justifications for eligibility criteria, even when 'self-evident'
 - Recruiters' understanding, buy-in
 - Transparency for everyone (including patients)
 - Could highlight opportunities for flexibility
 - Useful when something goes wrong
 - Justifying the required tests as well?
 - Explain inflexibility / show opportunities for flexibility
 - Explain use of subjective assessments

Conclusions & suggested way forward (3)

- Some practical things we can do now:
 - Review criteria for inclusiveness (INCLUDE*)
 - Document decisions around data collection and (central) monitoring
 - By whatever means (QC, training, templates) ensure basic issues avoided, e.g. clarity about tests required or timelines
 - Consider more rigorous methods based on risk (e.g. run-in periods, expert reviews, audit-feedback)

* <https://www.trialforge.org/trial-forge-centre/include/>

Conclusions & suggested way forward (4)

- Other future developments?
 - Site reviews of protocol drafts (improve clarity and feasibility? Help with training?)
 - Wider agreement on more detailed standards/standard elements?
 - Uses of computer-readable criteria:
 - Using draft criteria to review recruitment effects (NHS Digitrials)
 - Comparing current criteria to those from similar trials
 - Move away from same document fulfilling two purposes: transparency/operational manual?

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- All those who took 3-5 minutes to complete the recruiter survey



Questions?

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References for prevalence of eligibility errors

- **Simpson F**, Sweetman EA, Doig GS. A systematic review of techniques and interventions for improving adherence to inclusion and exclusion criteria during enrolment into randomised controlled trials. *Trials*. 2010;11
- **Yelland LN**, Kahan BC, Dent E, et al. Prevalence and reporting of recruitment, randomisation and treatment errors in clinical trials: A systematic review. *Clin Trials*. April 2018:174077451876162.
- **Stenning SP**, Cragg WJ, Joffe N, et al. Triggered or routine site monitoring visits for randomised controlled trials: results of TEMPER, a prospective, matched-pair study. *Clin Trials*. August 2018:174077451879337.
- **Brosteanu O**, Schwarz G, Houben P, et al. Risk-adapted monitoring is not inferior to extensive on-site monitoring: Results of the ADAMON cluster-randomised study. *Clin Trials*. 2017;14. doi:10.1177/1740774517724165
- **Wyman Engen N**, Huppler Hullsiek K, Belloso WH, et al. A randomized evaluation of on-site monitoring nested in a multinational randomized trial. *Clin Trials*. October 2019:174077451988161. doi:10.1177/1740774519881616
- **Statler A**, Othus M, Erba HP, et al. Comparable outcomes of patients eligible vs ineligible for SWOG leukemia studies. *Blood*. 2018;131(25):2782-2788. doi:10.1182/blood-2018-01-826693
- **Spragg RG**, Masys DR, Sergeant D, Lawrie T, Taut FJH. An informatics strategy to assure enrollment criteria compliance in studies of the critically ill. *Contemp Clin Trials*. 2010;31(6):530-535. doi:10.1016/j.cct.2010.07.006
- **Sweetman EA**, Doig GS. Failure to report protocol violations in clinical trials: a threat to internal validity? *Trials*. 2011;12:214. doi:10.1186/1745-6215-12-214