Patient Reported Outcomes
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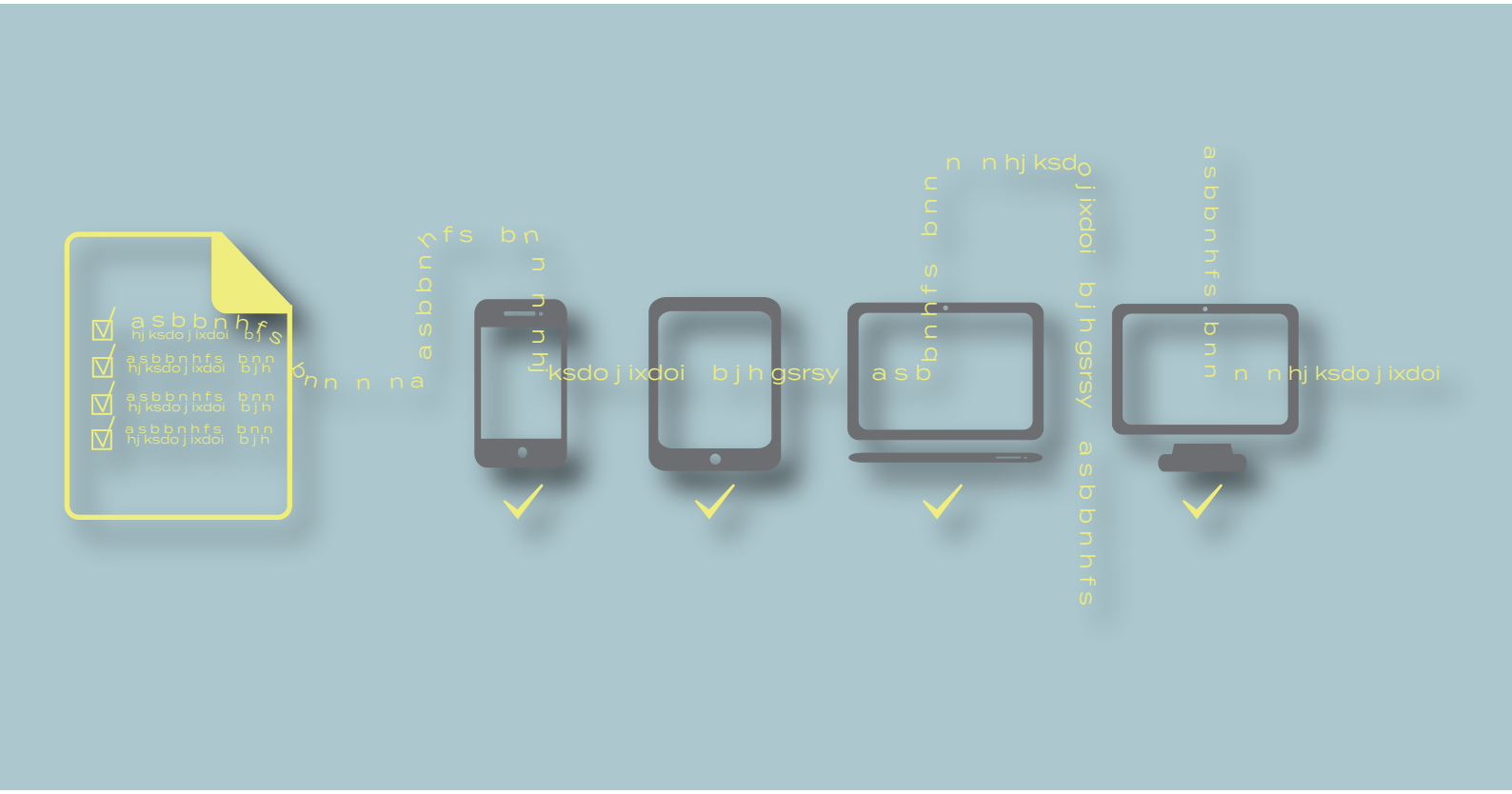
From Paper to ePROs

Good Practice Guide for Migration.



By: The Clinical Outcomes team at Oxford University Innovation

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1 What is this guide?

This support guide is for those planning to migrate one of our Patient Reported Outcome (PRO) Measures or PROMs to an electronic method of capture, or an ePRO. Although focussed on PRO Measures (or PROMs) this guide is applicable to any of our Clinical Outcome Assessments (COAs). This guide is also written to ideally cover our broad user base, which includes healthcare providers, academic researchers, device manufacturers as well as Pharmaceutical clients and CROs. This guide provides best practice guidance and examples for the migration of existing paper-based PROs to a screen based, visually presented ePRO. This guide does not cover changes to non-visual modes of ePRO such as Interactive Voice Response Systems (IVRS) or situations where more substantial changes to the PRO are being made beyond simply accommodating the change in modality. This guide is an introduction to good practices in ePROs and should you have any questions on the guide or its application then please do contact the Clinical Outcomes team at Oxford University Innovation.

What are ePROs? 2

ePROs are simply digitally reproduced versions of PROs that were originally developed (and validated) to be completed using paper and pen. For the purposes of this guide we focus on when validated PROs are completed by patients directly using a screen-based digital device, e.g. smartphone, tablet or PC screen.

ePROs have become the preferred method of capturing patient's responses. Some of the benefits that can be achieved by ePROs over paper and pen include:-

- Improved data quality
- Increased security
- Better respondent experience
- Administrative and cost benefits

3 Why is this guide and its teachings important?

Retaining the measurement properties of the original validated PRO is essential if we are going to be able to claim the resulting data are valid and equivalent to results acquired from the paper version. In some applications, for example where the resulting data is to be used in a regulatory environment such as with the FDA in the USA, then evidence of careful migration and testing of the ePRO is required when resulting data is to be used to support a label claim. Failure to recreate ePROs properly can alter the measurement properties of the PRO measure, possibly wasting a lot of time, effort and money for everybody involved. As owners / managers of the PRO measures licenced, we have a duty of care to ensure ePROs are equivalent to the original pen and paper completed PRO instruments.

Modifications of PROs to ePROs 4

The International Society of Pharmacoeconomics and Outcomes Research (ISPOR) guidelines specify that there are three levels of modifications when migrating a paper based PRO to an ePRO.

These are:

1) Minor modification – for example changing instruction text to suit the modality, e.g. instead of "Please tick one response" to "Please select one response"
2) Moderate modification
3) Substantial modification

This guideline focuses on minor modifications applicable to visual, screen-based reproductions of our measures as ePROs. The Clinical Outcomes team discourages users from making moderate and substantial modifications to its paper-based PRO measures as these changes require equivalence and full psychometric testing respectively, and may result in versions which are not comparable to the original validated paper-based PRO measure, making the comparison of data across studies difficult. However, if you are considering moderate or substantial changes to our measures, you must approach us about this at the earliest opportunity.

A minor modification is not expected to change the content or meaning of the items and response scales. The guidance provided here, such as changes to ePRO specific instructions (to suit the modality), and changes in the format, are considered to be minor modifications.

Moderate and substantial modifications may include changing the wording of the items, or response options. For confidence in the arising data from changes such as these, requires evidence through equivalence and full psychometric testing.

5 Important things to consider

Before you embark on developing your ePRO, ensure that you have permission from the copyright owner of the PRO measure you are intending to use and ensure you have informed them of your plans to recreate it as an ePRO. Some copyright holders will have additional requirements or guidance when their instruments are being migrated to ePROs. Also check to see if translations exist of the PRO for countries you wish to recruit respondents from. There can be additional benefits from seeking the PRO owner's permission as they may well provide official versions of the PRO, scoring guides / manuals, or even advice on ePRO migration. Approach the owner / developer / manager of the PRO measure as early as possible in order to get permissions to build an ePRO of their measure, do not leave it until the last minute.

The target patient population

Different patient populations may have different needs when they engage with an ePRO system. If respondents have difficulty with using an electronic device, how will they be supported, or how can the ePRO design accommodate the respondent population?

Patient burden

Is the migrated ePRO going to create additional burden for the respondent? It can be tempting to add further questions and scales into an electronic system, however if this becomes too burdensome to patients, data quality may suffer. It is also worth indicating how much time the ePRO will take to complete, for example by providing a progress bar.

Where is the ePRO going to be completed?

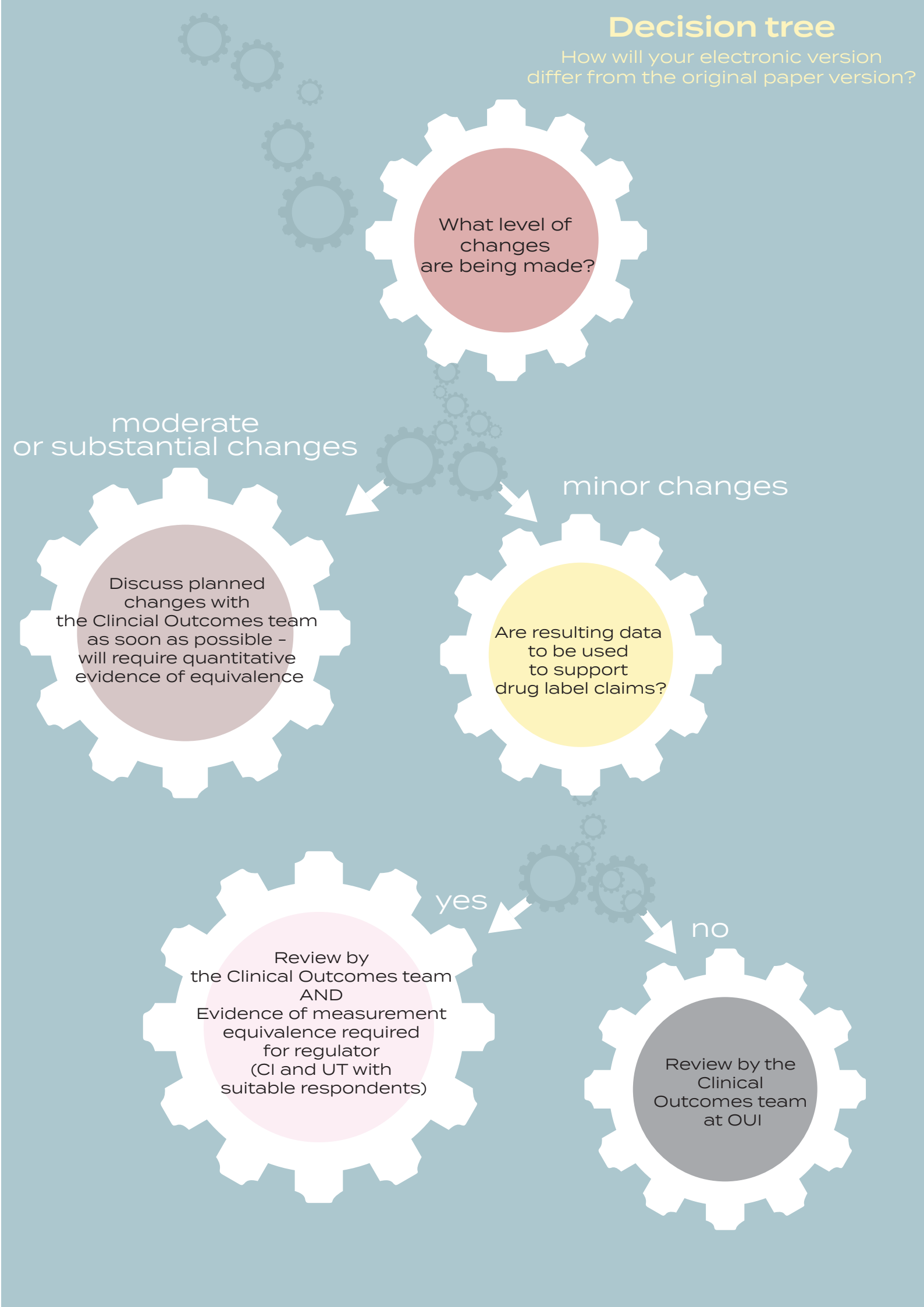
Is the ePRO going to be completed during a site visit or at the respondents' home? If the latter, then can you ensure that there will be no problems in the patient accessing the ePRO such as with logins, internet connection and their ease of use of a device without help.

PRO instrument to be migrated

Some PRO instruments are more straightforward to migrate than others. Does your PRO have complicated response options that may not migrate easily to a digital format? Would the migration alter the way in which respondents interpret what is being asked of them?

Decision tree

How will your electronic version differ from the original paper version?



What device will be used

Is the ePRO going to be completed on a tablet, PC or a smartphone? If it is to be completed on all device types, will the questions and response options be clear and easily answerable on all devices? The development of systems where the respondents own (familiar) mobile device is used to complete the ePRO is becoming popular. This type of system, that is agnostic to the device being used to complete the PRO measure, is referred to as Bring Your Own Device, or BYOD. Will the ePRO work on a range of operating systems such as Apple iOS, Android or Windows? Does it require an application (local app) to be downloaded? Are respondents expected to use their own device, and will they still be able to engage with the study if they do not have a device?

Data security

PROs can ask for personal details, and may include sensitive information. Are you sure that all collected data will remain secure, you have acquired the correct consents and have the same safeguards as paper questionnaires would? Will respondents be assured that their data is safe and secure? Are respondents aware of who to contact if they have questions or concerns?

Human error

Mistakes can happen when migrating the paper questionnaire into an electronic format. It is always worth having another person check that no errors have occurred, such as typos or missing questions. This situation is exacerbated when translations are being deployed as well, for example we expect translated versions of our PROs as ePROs to be proof-read by suitably qualified translators. There should also be checks to ensure that the questionnaire is coded correctly, so that results produced after completions are correct and accurate.

Who is going to develop the e PRO – you, a software developer or specialist ePRO (eCOA) vendor?

The answer to this question will impact the ease of development of the ePRO but also the budget. Doing it yourself may be cheaper but then all of the responsibility to accurately reproduce the ePRO falls on you and, depending on your level of expertise in ePROs, may be a challenging route. Similarly, if you are contracting a software developer to build the ePRO for you, you need to consider their experience in this niche field and their understanding of the requirements of this guide and ePRO good practices.

Guidance for Minor Modifications 6

Content of the ePRO

Consistent formatting

Ensure that formatting of the questions and response options are consistent with how they are presented in the paper version, and also the same across the ePRO. If part of the text in the paper PRO has underlining, bolding or italicising, ensure that this is presented the same in the ePRO. This does not mean you can't change the direction of responses though, for example instead of response options being presented horizontally on the paper version you may choose to present them vertically (but still in the same order) on the ePRO.

ePRO specific instructions

You may need to change the instructions and introduction of the ePRO to be more suitable for an electronic administration. For example, instead of asking respondents to 'circle an answer', you may have to change this to 'Please select one response' a good general phrase to use for all ePROs. If the ePRO is device agnostic (BYOD), ensure the instructions are also device neutral, for example not referencing 'clicking with your mouse' if the ePRO is also going to be completed on the touchscreen of a tablet.

5

Translatability

If the ePRO is going to be completed in different languages, the layout should be as consistent as possible depending on the language. The ePRO-specific instructions should be assessed to ensure that they will translate well into other languages being used, and have the same meaning as initially presented. A lot of ePROs are initially developed in English, with a plan to add translations at a later date, but many other languages require a lot more space than the English text, so ensure that during your design stage there is suitable space to accommodate translations if required.

Format of the ePRO

Layout

In an ePRO, ensure that instructions, the full item text and all of the response options are ideally all visible on one screen when respondents are considering the question. This may cause an issue with small screens, or long questions and a range of answer options. It is recommended that only one item per page is presented as this can reduce variability between devices and focuses the respondent's attention on a single question and response at any one time. If, for whatever reason, the questionnaire item is too large to fit in one screen, requiring scrolling, then ensure that is clear to the respondent. Do not allow a situation where the question and then some of the responses are above the fold, with some of the responses below the fold and at the same time allow first click responses without a separate Proceed button at the base of the question.

Be careful with the use of colours used in the ePRO. It is discouraged to use colours to indicate a 'right' or 'wrong' answer (using red and green, for example), and make sure that any contrast between colours is clear and won't be a problem for vision-impaired respondents.

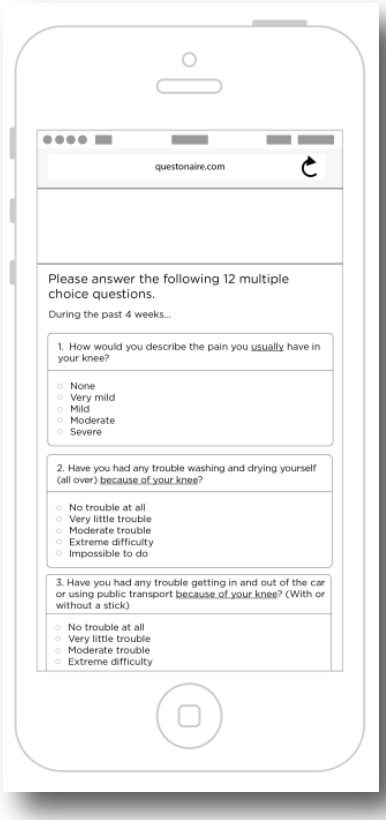
Response option order

All response options should be kept in the same order as they are presented in the original, paper PRO.

Suitable information required

Items may include specific instructions for completion that are usually visible for the entirety of answering a paper PRO, for example the recall period appearing at the top of the PRO. Once the ePRO is split up into multiple screens, it is important to ensure that respondents can still see and are reminded of the information throughout the ePRO. Consider putting the recall period or other instructions at the beginning of each item, for example repeating a common recall period "During the past 4 weeks……"- Failure to do this could easily lead the respondent to answer questions later in the questionnaire differently if they are no longer considering the common recall period.

example of poor ePRO



Usability of the ePRO

Appearance

If response options are too close together or too small, this can cause inaccurate data input and frustration for respondents, so ensure that the buttons are easy to select. Often ePRO systems will move onto the next question once a response option is selected, which is not recommended. Ensure that respondents are able to change their response option if they make a mistake or change their minds. The system should ideally remember responses so respondents can track backwards should they chose to alter their response at any time in the ePRO completion process. Some populations may have specific requirements. For example, those with poor eyesight will benefit from larger text. People with Parkinson's and with tremors as a symptom will benefit from larger differentiated response buttons.

Labelling

All response options should be clearly labelled with the original response. This should be checked on a range of screen sizes to confirm that the text and response option won't become detached or unclear to respondents.

Access procedure

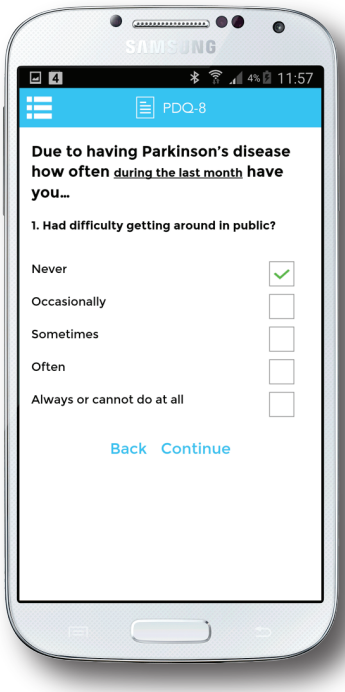
Make sure that respondents can easily access the PRO relevant to them from the landing page of the application or webpage. Include relevant and straightforward instructions to all respondents who may be accessing ePROs through this system.

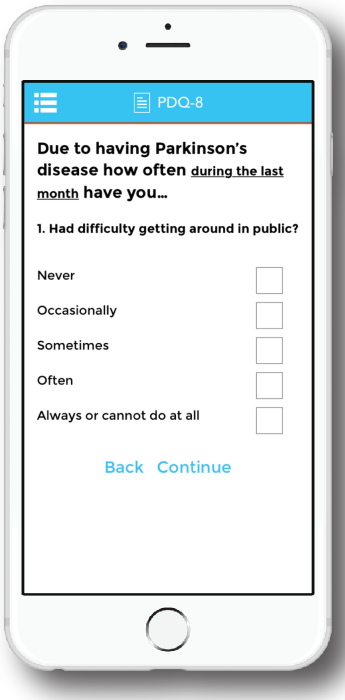
System issues

Respondents can find lag in the system frustrating and may lead them to abandoning or not engaging with the system as they should, which can lead to incomplete or inaccurate data. Make sure that the ePRO answer options are responsive and the system is quick and easy to navigate around.

Ease of navigation

It is advisable to let respondents go back to previous items and assess their answers, and also to easily navigate away from the application/window if they decide not to complete the ePRO. Again, make sure that the buttons to let them do so are easy to operate.





example of good ePRO

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Use of ePRO in a regulatory environment

If the data arising from the use of the ePRO is to be used with a regulator (in order to secure a label claim for example) then evidence of measurement equivalence of the ePRO is required. Good practice (Coons et al) suggests that some testing (cognitive debriefing and usability testing) of the ePRO on a small sample size (n=5 to 10 subjects) should be undertaken for ePROs that have undergone minor changes.

Cognitive Debriefing

Cognitive debriefing refers to a "think aloud" approach during which respondents in the target population complete the ePRO measure and are asked to describe in their own words what the instructions, questions and response options mean to them in their own words. Cognitive debriefing should be conducted with 10 respondents in the target population

The purpose of conducting cognitive debriefing following minor modification is to establish whether the mode of administration has in some way affected the respondent's interpretation of an item or response option. It is easy to assume that if an item hasn't changed then there should be no changes in interpretation.

Usability Testing

Usability testing is to examine whether respondents from the target population are able to use the device and software and complete the ePRO correctly. It is recommended that the respondent completes the ePRO in the presence of a researcher and follows a talk aloud process, explaining how they interpret the items and instructions as they work their way through the ePRO. The respondent should be encouraged to express any difficulties they are having or if any of the instructions are confusing. If any major problems become apparent it will be necessary to consider alternative instructions or changes to the software to resolve the issue(s), in which case the process of usability testing will need to be repeated.

7 Guidance for Moderate or Substantial Changes to PROs

If the PRO you are using needs moderate or substantial changes to be made, it is necessary to conduct full testing to ensure that the modified version achieves equivalence. Further advice should be sought from the instrument developers or authors and ePRO developers are recommended to undertake cognitive debriefing, usability testing, equivalence testing and/or full psychometric testing to ensure that their ePROs are valid.

Once the results of both cognitive debriefing and usability testing of minor changes have shown to produce equivalent results to the paper copy, the ePRO can then be administered to respondents. Substantial changes to a PRO need psychometric testing in addition as detailed below.

Equivalence Testing

Equivalence testing would assess how comparable results are from the paper PRO to the electronic PRO and uses quantitative methodology to ensure that scores from each administration do not vary significantly, which would suggest that the ePRO is performing differently and not measuring what the PRO is measuring.

Full Psychometric Testing

Changes to the PRO when migrating from paper to electronic can mean that the psychometric properties of the measure change, and so a full qualitative and quantitative psychometric evaluation is required. ISPOR guidelines state that at a minimum, this would include evidence for the internal consistency, test-retest reliability, and the construct validity of the ePRO in development.

What do Oxford University Innovation expect when migrating one of their PRO measures to ePRO?

This final chapter is aimed at assisting those who wish to reproduce and have respondents complete one of the Clinical Outcome measures available from Oxford University Innovation as an ePRO.

Approach Oxford University Innovation and request permissions to use the outcome measure you are interested in and indicate you wish to reproduce the measure as an ePRO. This can easily be achieved using our online licence request website here – http://process.innovation.ox.ac.uk/

During the online application to use the PRO measure, do make it clear (when prompted) what the purpose of the ePRO is, as this will influence the Clinical Outcomes team's response.

The Clinical Outcomes team will contact you to clarify a number of points about your plans to build an ePRO, before granting you a licence to develop the ePRO. The licence will include (as a minimum) our rights to review your electronic reproduction of our PRO measure, before being allowed to go live. If your use is part of a RCT, where the resulting PRO data is to be used to secure a label claim, may result in us working with you to secure evidence of equivalence (see end of section 6) in addition to our review.

You must then provide the Clinical Outcomes team with screenshots or ideally a working version of the ePRO so we can perform our review. We highly recommend you bring early versions (wireframes and early versions / screenshots) to OUI for our review. Bringing "finished / final" versions to us and expecting immediate / automatic sign-off (authorisation) is not recommended. Only after we have confirmed we have reviewed and are satisfied with your ePRO reproduction will we allow you (under the terms of the copyright licence) to use the ePRO routinely with respondents. We may provide a written review of your ePRO indicating changes that are recommended or required in order to pass our review. Failure to correct the required changes will result in the ePRO not being passed as an Authorised version and continued use is not allowed until the required changes have been made to our satisfaction and confirmed in writing.

On successful completion of the review we will recognise your ePRO as an Authorised ePRO reproduction and depending on the circumstances, and with your permission, may recognise your ePRO as an Authorised version on our website and other marketing materials.

Further reading

Byrom B, Tiplady B (eds.) ePRO: Electronic Solutions for Patient-Reported Data (2010) Farnham: Gower.

Coons SJ., Gwaltney CJ., Hays RD., et al. (2009). Recommendations on Evidence Needed to Support Measurement Equivalence between Electronic and Paper-Based Patient-Reported Outcome (PRO) Measures: ISPOR eRPO Good Research Practices Task Force Report. Value in Health 12(4); 419-429.

Gwaltney CJ, Shields AL, Shiffman S (2008). "Equivalence of Electronic and Paper-and-Pencil Administration of Patient-Reported Outcome Measures: A Meta-Analytic Review". Value in Health. 11 (2): 322–333.

US Food and Drug Administration. Guidance for industry: patient-reported outcome measures: use in medical product development to support labeling claims (DRAFT). February 2006.

One of the leading eCOA vendors is CRF Health who have a wealth of educational resources available on their website - http://resources.crfhealth.com

The Critical Path Institute (C-Path) has a PRO program called the PRO consortium, made up of thought leaders in the area of PRO instruments. Alongside this activity at C-Path is the ePRO consortium which also has a wealth of good practice documents on their website - https://c-path.org/programs/epro/

Our thanks to uMotif for their assistance in the production of this guide.
www.umotif.com

Contact us

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