

eCOOA

VS

COA:

Pros and Cons

By Olivier CHASSANY

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Kayentis

Dedicated to eCOA & Patient Engagement

Clinical Outcomes Assessment (COA) criteria include^[1]:

- 1/ Patient-Reported Outcomes (PRO)
- 2/ Clinician-Reported Outcomes (ClinRO)
- 3/ Observer-Reported Outcomes (e.g. patients or non-clinical caregivers) (ObsRO)

Author: Olivier Chassany, Patient-Reported Outcomes & Clinical Endpoints Methodology Research, at University Paris-Diderot 

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Electronic tools allow the collection of data (electronic Clinical Outcomes Assessments [eCOA]) from patients, physicians, observers (mainly parents), and caregivers using smartphones, tablets, or the internet. Over recent years, due to numerous advantages, such tools are increasingly preferred to paper questionnaires for primary and/or secondary endpoint data collection in clinical and epidemiological studies.

1.

● eCOA tools provide greater confidence in data quality and have major advantages for health authorities

- **ATTRIBUTABLE AND ORIGINAL:** the person (patient, physician, observer, caregiver) completing the questionnaire is identified using a unique code.
- **CONTEMPORANEOUS:** eCOAs allow confidence in the adherence to the schedules for questionnaire completion. These electronic tools record the exact time of completion, compared to paper questionnaires that have been shown in some studies to often be completed by patients outside the planned schedule ⁽¹⁾. Using

electronic tools the questionnaires have been shown to be completed on-time in more than 90% of cases, whereas timely completion by patients using paper questionnaires has been shown to occur in only 11% of cases ⁽¹⁾. By setting time intervals outside of which it is no longer possible to enter data, the risks associated with retrospective data completion are considerably reduced. The situation where a patient has omitted to fill out his or her self-assessment of symptoms on a daily basis as required and subsequently completes these data retrospectively using a paper system, often the day before or the day of the next study consultation, is no longer possible using eCOA.

- **ACCURATE:** As well as recording the exact time of completion, eCOA tools (using software logic checks and real-time edit checks) allow:
 1. A reduction in the amount of missing data by using reminders.
 2. A reduction in the amount of incomplete data by making a response to each question a requirement before being able to move on to the next question.
 3. The setting of limits for numerical data to avoid inconsistent data entries.

- **LEGIBLE:** Using eCOAs, unlike for paper questionnaires, there is no longer the problem of interpreting multiple responses to a given question when a single response is required. When numerous patients in a clinical study respond in an unclear manner using a paper questionnaire (e.g. when two response modalities are ticked instead of a single one) it can be necessary to develop a guide for interpretation (e.g. to use the value with the biggest change in order to record the worst case scenario). This can risk reducing the difference observed between two treatment groups, which could in turn result in insufficient power to detect a statistically significant difference (cf Figure EQ-5D). This eventuality cannot occur when using electronic tools. The same advantage is also evident for questionnaires completed by investigators, with writing that can be difficult to read being replaced by clear print.

- **LESS RISK OF LOST DATA:** the risk of losing data is reduced using electronic tools since eCOA data are sent immediately after completion to a server (with a back-up system), whereas paper questionnaires can be lost. If a patient loses a paper diary card, all the data contained in it will be lost (this could amount to several days or even weeks of data that can be lost); this is not possible using eCOA.

- **eCOA questionnaires are as valid (or more valid) than their paper equivalents:** this has been demonstrated in numerous equivalence studies ⁽²⁾. In a meta-analysis of 233 direct comparisons of electronic and paper questionnaires, the average mean difference was 0.2% (i.e. 0.02 points on a 10-point scale) and 93% of differences were within $\pm 5\%$ ⁽³⁾. When presented as correlation coefficients (ICC), the average weighted correlation coefficient was 0.9 and 94% of correlations were at least 0.75 ⁽³⁾.

2. Additional functionalities of eCOA compared to a paper equivalent

- **Easy patient access to a smartphone, tablet, or the internet** means that eCOA, and particularly ePRO, allow questionnaires such as diary cards to be completed more simply and on a more regular basis. There is no longer any need to attend regular consultations on site to ensure completion of the questionnaires ⁽⁴⁾.
- **Patients prefer an eCOA to a paper system.** When patients are asked which they prefer, after having completed the same questionnaires using electronic and paper systems, a large majority reports a preference for the electronic version ⁽⁵⁾. For example, in a pulmonary carcinoma study 60% of patients preferred to use electronic versions of the FACT-L and EQ-5D questionnaires, compared to 12% who preferred the paper version ⁽⁶⁾.
- **eCOA leads to a reduction in human error** in the management of the questionnaires. Paper questionnaires are still sometimes overlooked by some study staff, who may forget to provide the questionnaire or provide the wrong questionnaire; this is not the case for their electronic equivalents.

- **eCOA also provides a complete audit trail of all data** that are entered, with on-line monitoring and access to data in real time. This allows monitoring staff to be alerted to missing questionnaires for a particular person, or to data that are consistently missing for a group of persons, to understand the reasons for the missing questionnaires and/or data, and so to be able to implement the appropriate corrective action(s).
- **eCOA, and particularly ePRO, increases confidentiality and privacy** for patients who might otherwise have to complete a paper questionnaire during a site visit, since data entered using an electronic tool are sent directly to a server and cannot be seen by study site staff whereas data completed using a paper questionnaire (unless placed immediately by the patient in a sealed envelope) can potentially be seen by site staff. This is a particularly useful aspect of electronic data collection for private or sensitive data, such as a patient's opinion of the doctor-patient relationship, patient satisfaction with the treatment provided, or other questions for which a patient may not want to share the response with site staff (e.g. his or her compliance to the treatment regimen).
- **Electronic eCOA tools allow automatic and immediate score calculations** (immediate automated score), which can be very useful when eCOA tools are used for patient inclusion criteria. For example, verification of a diagnostic score from a questionnaire completed by an investigator or of symptom severity from a questionnaire completed by a patient; in these cases, a patient may not be included in a study if such a score is not above a certain threshold or within a pre-defined limit. Additionally, eCOA tools can be used to present these data to the investigator, the patient (e.g. to show a patient the change in a particular score over time), or monitoring staff.
- **eCOA can reduce the number of questions** for personalised questionnaires or when item response theory (IRT) modelling is used, allowing conditional navigation through the questionnaire by which items may be skipped depending on earlier responses. This adaptation is evident for electronic questionnaires, which is not always the case for paper questionnaires.

- **eCOA, and particularly ePRO, allows the participation of patients in clinical studies to be more reassuring.** Certain patient responses or a score at completion of a questionnaire, which could be suggestive of a worsening of a particular problem, can result in an automatic message for the patient and/or an alert for the investigator to take appropriate action. This can be particularly important, for example, during regular monitoring in studies with a risk of patient suicide, using the Columbia Suicide Severity Rating Scale (C-SSRS) ⁽⁷⁾. The electronic version of this questionnaire (eC-SSRS) has been shown to be better able to detect suicidal behaviour than the equivalent paper version ⁽⁷⁾.
- **Other than their use in clinical and epidemiological studies, eCOA tools, and particularly ePRO, are increasingly being integrated into clinical practice ^(8,9), allowing the automatic calculation of patient scores to share with both the patient and doctor, to present the evolution of such scores over time in graphical format with the aim of improving doctor-patient relationships and thereby to allow the doctor to discuss clearly aspects of daily life that are affected by the patient's illness. It should be noted that these electronic tools may require integration with other systems in use at study sites to optimize their use for all stakeholders.**
- **Finally, there is an advantage that needs to be better appreciated: electronic tools allow a reduction in the variability of a particular parameter** compared to using paper questionnaires. This has been shown in a urinary incontinence study in which the standard deviation of the number of episodes of incontinence was reduced by 30% when using an ePRO questionnaire compared to a paper equivalent ⁽¹⁰⁾. This has a direct impact on the statistical power of a study, e.g. in the above example, the magnitude of the effect was increased by 50% ⁽¹⁰⁾. So by the same token, the use of electronic rather than paper questionnaires would allow the requisite number of patients to be reduced or to have more power for the demonstration of a statistically significant difference. This clearly has a positive impact on not only study logistics but also on the overall cost of a study.

3. Potential drawbacks?

- **There was an initial reticence from health authorities** (e.g. FDA) regarding eCOA data, largely based on the view that PRO/OBsRO/ClinRO questionnaires do not comprise source data, although this is also true of the paper equivalents. However, the FDA has since published a guideline that recognises eCOA data as electronic source data with the same status as clinical study data collected using an electronic Case Report Form ⁽¹¹⁾. The FDA has now clarified that the electronic capture of clinical study source data is preferred to paper-based data collection ⁽⁴⁾.
- **eCOA is costly:** the cost of buying the electronic devices, development of electronic questionnaires, and storing and maintaining data on the server is more expensive than simply photocopying paper versions of the same questionnaires. However, the use of eCOA eliminates or reduces direct costs such as data entry, site monitoring of questionnaires, and data management and associated queries since these are done automatically during electronic questionnaire completion (and in any case an uncompleted, or poorly completed questionnaire cannot be modified after the event). Moreover, the advantages that eCOA brings to a clinical study in terms of better data quality (e.g. fewer missing data, better adherence to timely completion of questionnaires) should be taken into account.
- **Is eCOA truly attributable?** Compared to the completion of a paper questionnaire by a patient during a study visit with the investigator, when it is clear exactly who has completed the questionnaire, it is not possible to be absolutely sure who has replied to particular questions when a tablet is used at home. For example, the patient could have given his or her login details to someone else. But this is a greater issue for paper questionnaires completed at home since these are clearly not password-protected. So an eCOA and its associated login details give a better guarantee than the paper equivalent that the correct person has completed the questionnaire.

- **Certain patients are not able to completed electronic questionnaires:**
 - Elderly patients: this is less and less of a problem; increasingly the elderly are proficient on-line, and some studies even show better compliance by the elderly with scheduled times for questionnaire completion than younger adults.
 - Children: as for the elderly, studies for children show more and more advantages of electronic questionnaires compared to their paper equivalents, with children being familiar with tools such as smartphones and tablets from a very young age ⁽¹²⁾.
 - Certain pathological, e.g. psychiatric, conditions: again, studies show that electronic tools are equally feasible as their paper equivalents, e.g. in schizophrenic patients ⁽¹³⁾.
- **There is still resistance to electronic administration in the healthcare environment, and there is a necessity for training clinical staff, researchers and patients ⁽¹⁴⁾.**
- **There are technical difficulties in implementing electronic devices in research sites:** e.g. the use of tablets in hospitals where there is no WiFi or where there is restricted access to the hospital network ⁽¹⁵⁾.

The wide use of eCOAs in clinical trials has largely confirmed the theoretical advantages of electronic over paper questionnaires, including improved data quality and better confidence in these data. These are important factors in the efficient evaluation of submission dossiers by health authorities for approval and reimbursement. Electronic COAs will continue to be developed and will increasingly replace paper clinical study documentation (e.g. electronic patient information and consent documents).

Example

Based on an international, pivotal Phase III study in which one of the PRO paper questionnaires was the EQ-5D questionnaire: the following figures present examples of inadequate patient responses that required the sponsor to produce a guide to interpretation during the study to define how to report these responses and which value to use in the statistical analyses.

Under each heading, please tick the ONE box that best describes your health TODAY.

MOBILITY

I have no problems in walking about

I have slight problems in walking about

I have moderate problems in walking about

I have severe problems in walking about

I am unable to walk about

SELF-CARE

I have no problems washing or dressing myself

I have slight problems washing or dressing myself

I have moderate problems washing or dressing myself

I have severe problems washing or dressing myself

I am unable to wash or dress myself

USUAL ACTIVITIES (e.g. work, study, housework, family or leisure activities)

I have no problems doing my usual activities

I have slight problems doing my usual activities

I have moderate problems doing my usual activities

I have severe problems doing my usual activities

I am unable to do my usual activities

PAIN / DISCOMFORT

I have no pain or discomfort

I have slight pain or discomfort

I have moderate pain or discomfort

I have severe pain or discomfort

I have extreme pain or discomfort

ANXIETY / DEPRESSION

I am not anxious or depressed

I am slightly anxious or depressed

I am moderately anxious or depressed

I am severely anxious or depressed

I am extremely anxious or depressed

The best health you can imagine

100

95

90

85

80

75

70

65

60

55

50

45

40

35

30

25

20

15

10

5

0

The worst health you can imagine

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine. 0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY =

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Glossary

The term 'person' covers anyone who may be required to complete an eCOA questionnaire: patient, investigator, observer (e.g. patient), or caregiver.

ClinRO:	Clinician-Reported Outcomes
COA:	Clinical Outcomes Assessment
eCOA:	electronic Clinical Outcomes Assessment
ePRO:	electronic Patient-Reported Outcomes
FDA:	US Food and Drug Administration
ICC:	intraclass correlation coefficient
ObsRO:	Observer-Reported Outcomes
PRO:	Patient-Reported Outcomes

