The Importance of Quality Checks for Digital Health Studies Using Remote Unsupervised Assessments to Study Functional Impairment in MS

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KEY FINDINGS

QUALITY CHECKS ENABLE EFFICIENT ASSESSMENT OF ACCORDANCE WITH INSTRUCTIONS IN REMOTE, SELF-ADMINISTERED TESTS OF FUNCTIONAL IMPAIRMENT IN MS

Quality checks are crucial to prevent future non-accordant tests (tests not taken according to their instructions) via alerts, hence improving data quality, and inform data analysis by enabling exclusion of non-accordant tests in sensitivity analyses

Quality checks → Improve data collection → Inform data analysis

BACKGROUND

- Remote digital assessments of MS offer an opportunity to increase the frequency and ecological validity (relevance for daily life) of measurements and can complement in-clinic assessments
- While a recent study has shown that participants remain adherent to high-frequency measurements over 24 weeks,[1] the remote setting increases the risk of non-accordant tests not being detected, potentially leading to incorrect conclusions from the collected data

Remote digital assessments of MS

Challenge
Detection of non-accordant tests (tests not taken according to their instructions)

***Solution* → Quality checks**
Digital features providing information about how the test was executed:
- To act as accordance indicators
- To ensure data quality
- To inform data analysis

Quality checks developed as indicators of non-accordant tests

Phone on Table
Detects whether the phone was left on a fixed surface instead of attached to the body during gait tests[2]

Skipping
Detects whether the user was tapping on the screen to skip a shape instead of drawing it as instructed

Play to Quit
Detects whether the user was trying to exit the test rather than perform it as instructed

Objective:
To investigate quality checks for data collected during remote digital assessments of MS with the aim of:
- Examining the prevalence of non-accordant tests
- Evaluating the impact of interventions[a] for preventing non-accordant tests

[a]'Intervention' refers to a follow-up with the user to inform them on how to correctly perform the test. In this analysis, the interventions are simulated after the fact, rather than performed during the study.

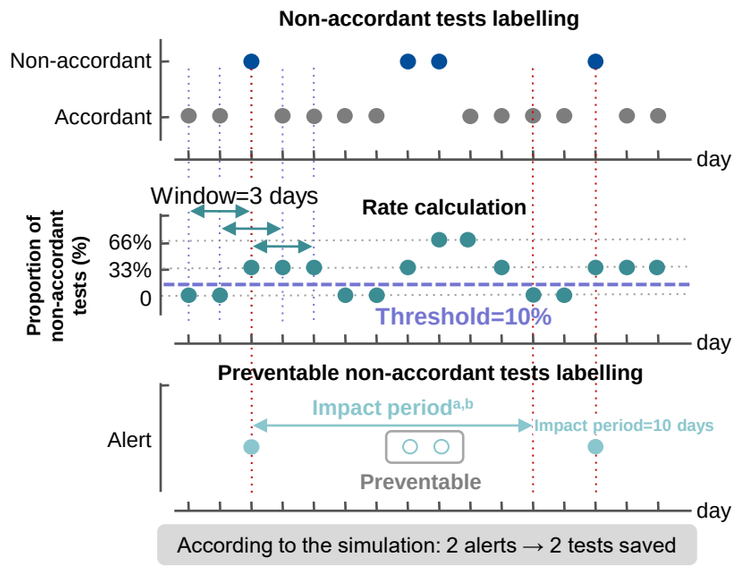
METHODS

Dataset and Alerts Triggering Logic

- CONSONANCE is an open-label, single-arm, 4-year study to evaluate effectiveness and safety of ocrelizumab treatment in patients with PMS (NCT03523858)
- The prevalence of test runs flagged by the 'Phone on Table', 'Skipping' and 'Play to Quit' indicators were assessed in daily digital tests (using a precursor app to Floodlight™ MS) of gait, hand motor function and weekly cognition in the CONSONANCE study for a subset of 427 PLwMS
- Observations were made from treatment start date until September 2020 (average and maximum observation lengths are 66 and 117 weeks, respectively)
- Interventions were simulated in CONSONANCE for each participant by triggering "alerts" based on the proportion of non-accordant tests as detected by the quality checks
- After an alert, the participant was assumed fully accordant for a certain time interval (impact period) and any non-accordant tests during this window were counted as preventable non-accordant tests
- Definitions of the tests and quality checks can be found via the QR code

Alerts Triggering Logic: Simulation

Data: Tests marked as accordant/non-accordant by the quality checks



Simulation steps:

1. **Rate calculation:** Proportion of non-accordant tests calculated in a given time window as: **[number of non-accordant tests within the window]/[window length]**
2. **Threshold approach:** Alerts are triggered whenever the rate is larger than the threshold
3. **Preventable non-accordant tests identification:** Tests occurring within the impact period and marked as non-accordant, in reality, are considered as preventable

[a]The impact period started on the day of the alert/intervention, as it allowed immediate notification to the user and precise recording of the events;
[b]The simulation is based on the optimal situation where all tests executed after an intervention (during the impact period) are accordant.

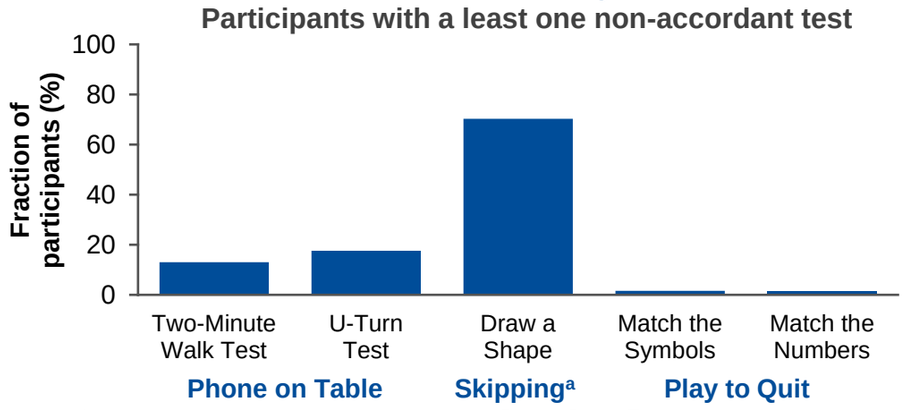
RESULTS

Prevalence Analysis and Impact of Interventions

- In total, 373,860 tests were analysed in CONSONANCE; 1.1% of these tests were non-accordant (more data on the simulations and information on the tests and quality checks can be found via the QR code)
- Simulation parameters (window [10 days], threshold [20%], impact period [30 days]) were optimised taking into account a trade-off between the number of interventions and the number of preventable non-accordant tests

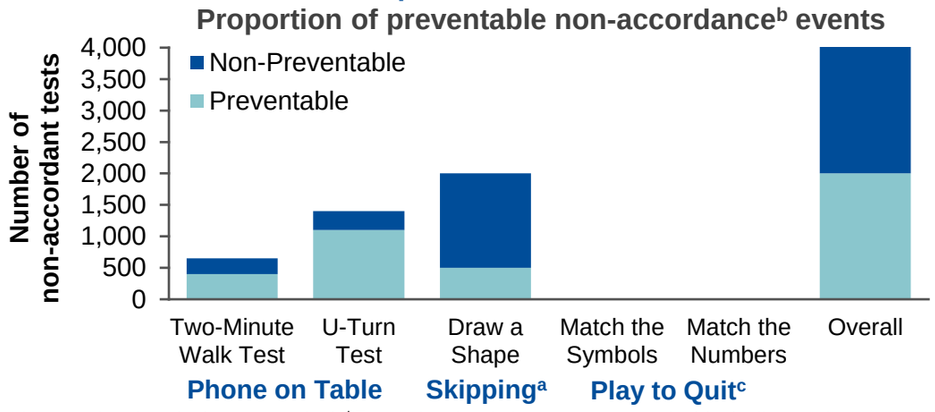
Prevalence analysis

Participants with a least one non-accordant test



Impact of interventions

Proportion of preventable non-accordance[b] events



Simulating alerts based on a 20% threshold within a 10-day window and considering an impact period of 30 days **reduced the overall number of non-accordant tests by up to 51%**

[a]Prevalence of at least one non-accordant test is higher for the Draw a Shape Test as it is easy to accidentally tap a shape and make a test non-accordant; [b]For each subject showing non-accordant tests, the number of non-preventable tests was at least one; [c]Not enough non-accordant tests were observed to prevent any.

Abbreviations
MS, multiple sclerosis; PLwMS, people living with multiple sclerosis; PMS, progressive multiple sclerosis.

References
1. Midaglia L, *et al. J Med Internet Res* 2019;21:e14863;
2. Montalban X, *et al. Mult Scler* 2021;13524585211028561.

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Disclosures
A Festanti is a contractor of F. Hoffmann-La Roche Ltd via Randstad. **M Zanon** is an employee of F. Hoffmann-La Roche Ltd. **F Dondelinger** is an employee of F. Hoffmann-La Roche Ltd. **F Lipsmeier** is an employee of F. Hoffmann-La Roche Ltd. **X Denos** is a contractor for F. Hoffmann-La Roche Ltd via Hays. **S Hubeaux** is an employee and shareholder of F. Hoffmann-La Roche Ltd. **M McGinley** reported serving on scientific advisory boards for Genzyme and Genentech; receiving research support from Novartis; and receiving funding from a KL2 (KL2TR002547) grant from Clinical and Translational Science Collaborative of Cleveland, from the National Center for Advancing Translational Sciences component of the National Institutes of Health. **G Comi** in the past year has received compensation for consulting services from Almirall, Chugai, EXCEMED, F. Hoffmann-La Roche Ltd, Forward Pharma, Genzyme, Merck, Novartis, Receptos, Sanofi and Teva; and compensation for speaking activities from Almirall, EXCEMED, F. Hoffmann-La Roche Ltd, Genzyme, Merck, Novartis, Receptos, Sanofi and Teva. **L Craveiro** is an employee of F. Hoffmann-La Roche Ltd. **M Lindemann** is a consultant for F. Hoffmann-La Roche Ltd via Inovigate. **H Butzkueven** has received institutional (Monash University) funding from Biogen, F. Hoffmann-La Roche Ltd, Merck and Novartis; has carried out contracted research for Biogen, F. Hoffmann-La Roche Ltd, Merck and Novartis; has taken part in speakers' bureaus for Biogen, Genzyme, F. Hoffmann-La Roche Ltd and Merck; has received personal grants from Oxford PharmaGenesis and Biogen (prior to 30 June 2018).

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SUPPLEMENTAL MATERIAL

A Festanti,[1] M Zanon,[1] F Dondelinger,[1] F Lipsmeier,[1] X Denos,[1] S Hubeaux,[1] M McGinley,[2] G Comi,[3] L Craveiro,[1] M Lindemann,[1] H Butzkeuven[4]

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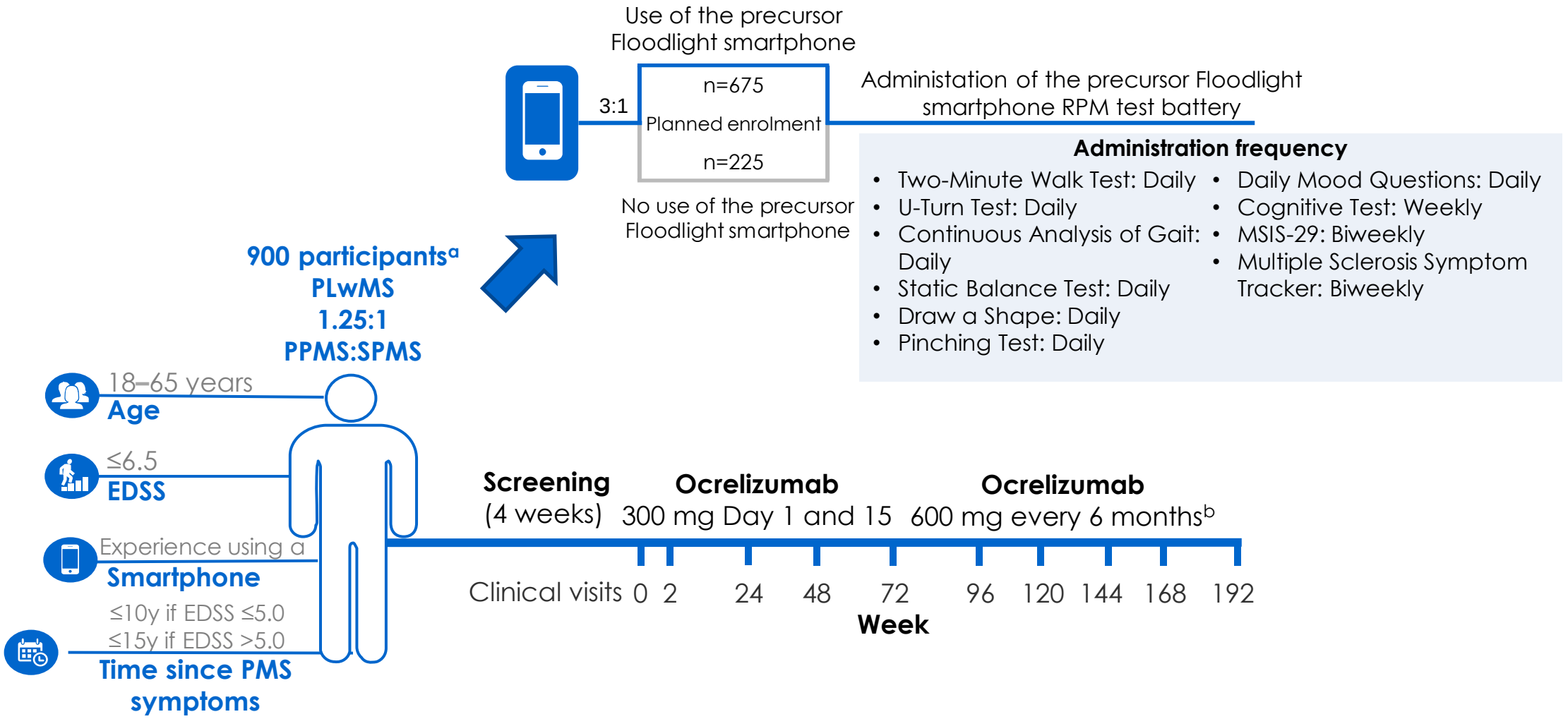
Supplemental Material

- Background: CONSONANCE Study Design
- Overview of the Floodlight™ MS Smartphone Application
- Floodlight in CONSONANCE Overview Slide
- Definitions of the Tests
- Definitions of Quality Checks
- Simulation to Evaluate the Impact of Interventions on Non-Accordant Tests
  Case Study: U-Turn Test and Phone on Table Quality Check

Background: CONSONANCE Study Design



Administration frequency

- Two-Minute Walk Test: Daily
- U-Turn Test: Daily
- Continuous Analysis of Gait: Daily
- Static Balance Test: Daily
- Draw a Shape: Daily
- Pinching Test: Daily
- Daily Mood Questions: Daily
- Cognitive Test: Weekly
- MSIS-29: Biweekly
- Multiple Sclerosis Symptom Tracker: Biweekly

ClinicalTrials.gov Identifier: NCT03523858

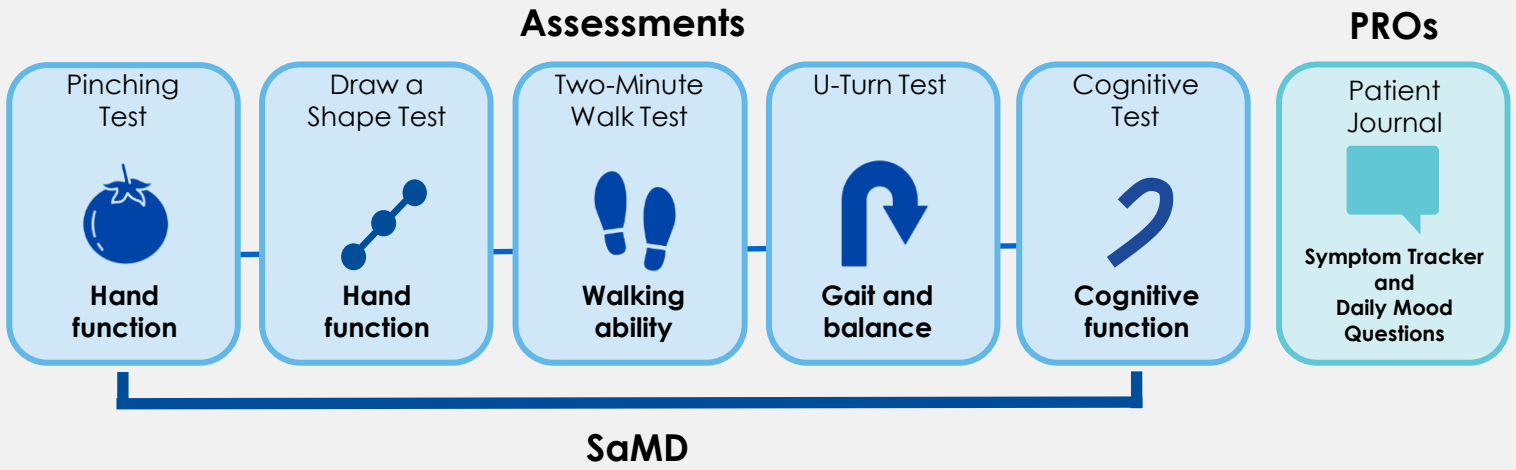
Participants who discontinue treatment after Week 144 will be followed up for ≥48 weeks after early treatment discontinuation evaluation visit, and not after last infusion of study drug. Patients who withdraw from study drug and switch to commercially marketed ocrelizumab, either after completion of the 192-week treatment period or after early discontinuation of the 192-week treatment period, will not enter the safety follow-up period.

[a]Participant numbers represent planned enrolment numbers; [b]Up to a maximum of eight doses.

EDSS, Expanded Disability Status Scale; MSIS-29, Multiple Sclerosis Impact Scale-29; PLwMS, people living with multiple sclerosis; PMS, progressive multiple sclerosis; PPMS, primary progressive multiple sclerosis; RPM, remote patient monitoring; SPMS, secondary progressive multiple sclerosis; y, years.

Overview of the Floodlight™ MS Smartphone Application

- Floodlight MS is a digital solution for remote assessment in multiple sclerosis (MS) for use in clinical practice, comprising five software as a medical device (SaMD) assessments and a Patient Journal



- Different precursors of the Floodlight MS assessment suite have been used in studies such as CONSONANCE

MS, multiple sclerosis; PRO, patient-reported outcome; SaMD, software as a medical device.

Floodlight in CONSONANCE Overview Slide

Study design

Study population:
427 PLwMS, with PPMS or SPMS, enrolled in the CONSONANCE study are using a precursor of the Floodlight MS assessment suite

Assessments:
Clinical, PROs, digital biomarkers, MRI, serum/plasma/CSF biomarkers

CONSONANCE study objectives for the Floodlight programme

To gather data that will increase the understanding and meaningfulness of the precursor Floodlight assessments:

- Evaluate the association between Floodlight assessments and clinical outcomes, PROs and subclinical disease activity

To measure patient adherence to and satisfaction with the Floodlight assessments and application

To gauge any learning/practice effects

CSF, cerebrospinal fluid; MS, multiple sclerosis; PLwMS, people living with multiple sclerosis, PPMS, primary progressive multiple sclerosis; PRO, patient-reported outcome; SPMS, secondary progressive multiple sclerosis.

Definitions of the Tests

Two-Minute Walk Test: The user is instructed to walk quickly for 2 minutes
Measures: Stamina and endurance

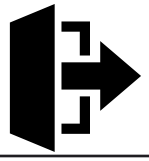
Draw a Shape: The user draws six different increasingly complex geometric shapes with their finger on the touchscreen of their smartphone
Measures: The speed and accuracy of hand and finger movements

Match the Symbols/Match the Numbers:[a]
The user is instructed to match the corresponding symbols and numbers
Measures: How quickly the user processes information

U-Turn Test: The user is instructed to walk and perform five consecutive 180° turns at least 4 meters apart
Measures: How quickly the user can turn while walking

[a]The Match the Symbols/Match the Numbers Tests are sub-tests of the Cognitive Test in Floodlight MS.

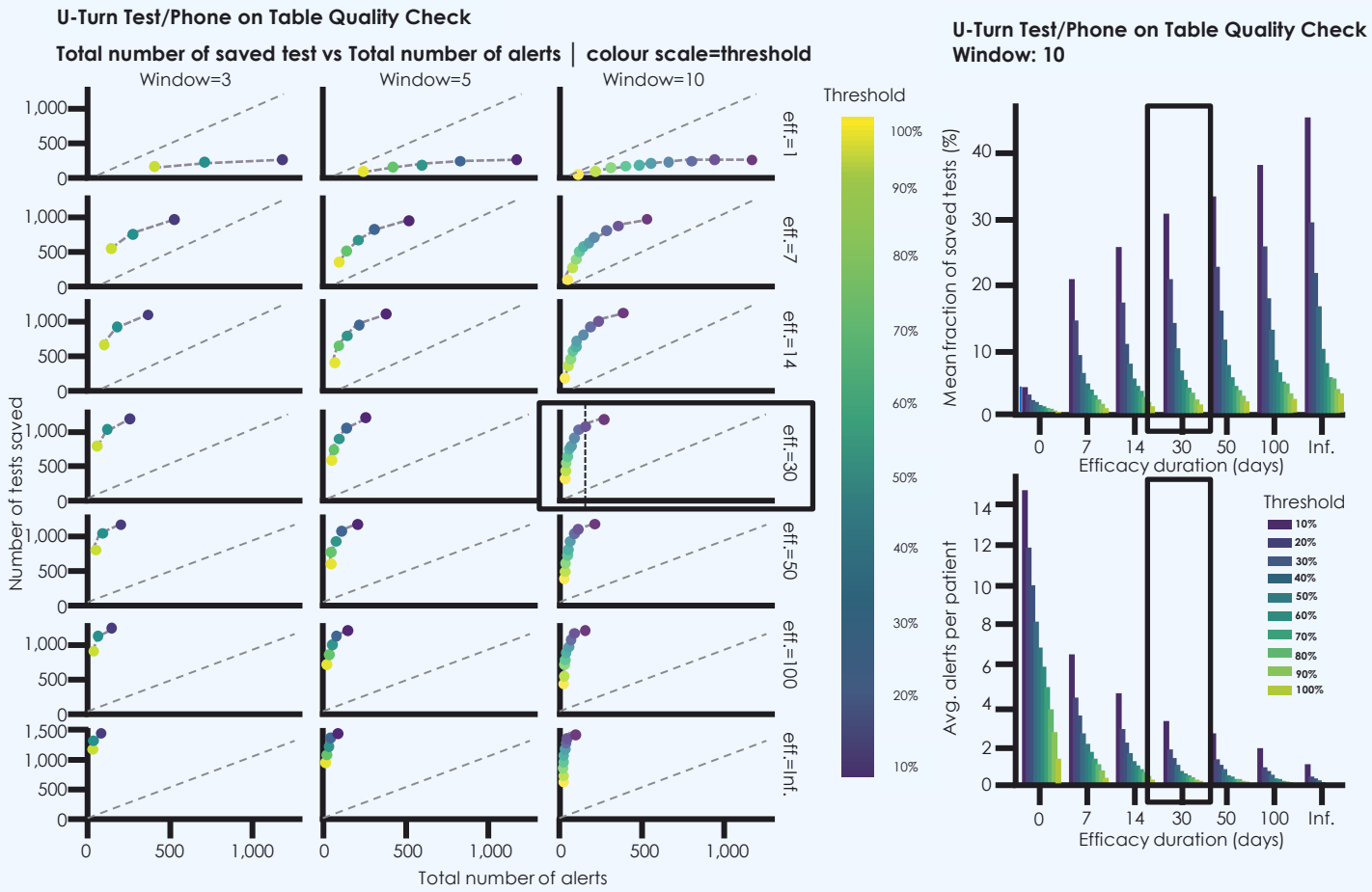
Definitions of the Quality Checks

Quality check indicator	Relevant active tests	Description	Implementation
Phone on Table 	Two-Minute Walk Test, U-Turn Test	Phone on Table detects whether the phone was left on a fixed surface instead of attached to the body while performing gait tests, thus whether data about movement could not be collected.	**Horizontalness:** Average ratio between the component of the acceleration parallel to gravity and the acceleration magnitude. **Orientation stability:** Standard deviation of the ratio between the component of the acceleration parallel to gravity and the acceleration magnitude. Horizontalness >0.998 and orientation stability <0.005.
Skipping[a] 	Draw a Shape Test	Skipping detects whether the user was tapping on the screen to skip the drawing of at least one out of the six shapes proposed, thus whether data related to hand motor function could not be collected.	Trace duration, hits accuracy and length ratio<minimum value for any of the shapes.
Play to Quit 	Match the Symbols/Match the Numbers	Play to Quit detects whether the user was trying to exit the test rather than perform it, thus whether data related to cognitive function could not be collected.	Accuracy rate and average time to choose and answer<minimum values.

[a]Skipping is a more sensitive quality check to accidental misexecution for the Draw a Shape Test than Play to Quit, as Skipping is triggered for a test even if it was detected for only one out of the six shapes proposed.

Simulation to Evaluate the Impact of Interventions on Non-Accordant Tests Case Study: U-Turn Test and Phone on Table Quality Check

The impact of interventions, aimed at informing the patient on how to properly execute the tests, has been assessed by simulating alerts based on the rate of non-accordant tests detected in data from the CONSONANCE study.



- For each participant, an alert/intervention is triggered when the rate of non-accordant tests within a certain time window hits a given threshold
- All non-accordant tests occurring after an alert and within a certain impact period are counted as saved/preventable
- The total number of alerts depended on the sample size (i.e. the size of the population) and on the parameters of the simulation, including the window length, threshold value and impact period length
- At fixed values of the simulation parameters, the number of alerts depended also on the frequency or distribution in time of non-accordant tests
- When there is no limit on the impact period (eff.=Inf.), a single alert is sufficient to prevent all future non-accordant tests, and hence the maximum total number of alerts is equal to the number of non-accordant participants (75 for the U-Turn Test)
- The optimal values of the window length and of the rate threshold were estimated by considering a trade-off between the number of alerts for various lengths of the impact period
- For the U-Turn Test and Phone on Table Quality Check, the optimal values of the parameters obtained from the simulation that could be used by an algorithm triggering interventions to inform patients were: window=10 days, threshold=20%

The simulation procedure has been applied to the data available from the other active tests/quality checks and the optimal parameters estimated by applying the same strategy as explained here for U-Turn Test and Phone on Table. The resulting impact of interventions is reported in the poster Results.
Avg., average; Eff., efficacy; Inf., infinite.