Appendix S1

METHODS: DEVELOPMENT OF ITCHAPP©

Development of ItchApp© began in June 2013. The first step consisted of specifying the requirements that define the basis of the eDiary with information provided by clinicians experienced in clinical trials (SST, AT, CZ). The goals were identified as follows: (*i*) the app should be easy to use for the subject (high user friendliness) and more attractive than paper-based alternatives, (*ii*) the app should provide a demonstration mode (demo) and be simple for the physician to launch for a new subject, (*iii*) data should be made available for the researcher in both a neat and secure format, (*iv*) data entry should take place once per day and the resulting data should be available in real-time. To this end, we worked with Arone, an IT company, in order to optimize collection and analysis of subject data and develop database applications for clinical trials. In addition, the data quality requirements and device regulations were analysed by a third-party CRO (Dermlink International Ltd, London, UK). A document containing analysis of the data and technical solutions was then generated.

A consensus was reached regarding the use of smartphones as the sole electronic devices for data entry in the validation study. At this point in development, study subjects were not allowed to use the app on their personal smartphones because ItchApp© still required validation. Subjects were unable to access or alter the provided smartphone settings due to study-specific restrictions, thus providing yet another advantage. The application could be further validated by eliminating influences by different types of smartphones. The use of a native application for Android was taken into consideration due to their wide use and the cost of the devices that would be provided to subjects. It was decided to include offline capabilities to ensure that data could be entered anytime and anywhere. Arone's eCRF Projection® platform served as a central database and web application for accessing synchronized data and managing sites. Microsoft Visual Studio and Xamarin are software development programmes used in the app's development and web service for synchronization. Development was completed within 2 months.

The Android application was the main development tool. Multiple steps were taken in favour of simplifying data entry, as follows:

- Data entry was designed with equal online and offline capabilities. The entered data is stored in a local database before being synchronized with the central database.
- A subject is registered in the central database for the clinical trial with his or her trial ID, and the phone is set up by the physician selecting this ID. The subject is not subsequently required to enter any personal information or a username, but to use a password to validate the data entry in order to remain compliant as per Title 21 CFR Part 11 (S1).
- The method of data entry is simple and consists of 1 question per page. Input masks and push buttons on the scales are also available. The subject can modify their entries until they provide a signature.
- The subject can input answers up to 3 days after the due date.
- The data is automatically synchronized when the system is online.

ItchApp© is in full compliance with current regulations (e.g. privacy, electronic signatures and automated audit logs) and research standards (e.g. security and data loss prevention). The web service was developed for data synchronization to the central database. The Projection eCRF has been adapted for reading and printing data, exporting statistics and site management (S1).

The application was fully tested and validated by Arone with Good Automated Manufacturing Practice Forum 5 (GAMP) (e.g. the validation protocol, risk analysis, test scripts, traceability matrix) prior to use. A procedure register of the application and data transfers to the central database were made in accordance with the Federal Data Protection Act (Bundesdatenschutzgesetz, §10, Abs. 3) of North Rhein-Westphalia and approved by the local ethics committee (No. 2013-584-f-A) and the authorized data protection representative of the University of Münster.

SUPLEMENTARY REFERENCE

S1. CFR - Code of Federal Regulations Title 21". U.S. Food & Drug Administration. U.S. Food & Drug Administration. Retrieved 15 September 2016.