Expert Rater Assisted Score Evaluation (ERASE): A New Method to Enhance Signal Detection in Randomized, Placebo-Controlled, Clinical Trials

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Abstract

Background: Numerous factors related to the design, conduct and evaluation of randomized clinical trials (RCTs) have been considered over the years to account for the relatively high placebo response rate in psychiatric diseases [1-3]. Surprisingly little attention has been given to the process of data collection itself, i.e. the clinical interview and correct interpretation of a patient's condition [4]. Here we exhibit a new method, involving expert rater assisted score evaluation (ERASE), developed and implemented for the first time in a multinational RCT in schizophrenia, with the aim to control for interview quality and enhance signal detection.

Methods: The process behind ERASE is based upon collaboration between investigators, or Site Raters (SR) and Independent Raters (IR). A laptop with an inbuilt camera is deployed by SR for recording of interview sessions and collection of collateral information. Recorded interview sessions are transmitted along with the collateral information over the web to a secure server. IR (blind to SR ratings) reviews the recorded video via the Internet, evaluates interview quality by completion of the Rater Applied Performance Scale (RAPS), and uploads his/her scores on the applicable rating scales (here PANSS and SANS) to the website. The uploaded IR scores are reviewed by SR who may subsequently adjust their own ratings before final submission of data to the sponsor.

Results: 215 patients across 25 sites in Europe, Russia, and Latin-America provided informed consent, were randomized and evaluated using ERASE. The method was well accepted by ethics committees, investigators and majority of patients, and proved to be technically feasible. Comparisons between SR and IR ratings demonstrate that ERASE can be used to minimize the impact of inconsistent investigator performance on trial outcome.

Conclusions: ERASE entails a novel and promising approach to boost the power of a RCT by improving the signal/noise ratio. Through continuous calibration of the clinical assessments, the method may reduce noise caused by non-structured interviews and investigator bias. At the same time, drug effects may be amplified through more focused patient evaluation.

Source of Funding: ERASE (patent pending) was invented by Organon (nowadays part of Schering-Plough) and implemented in partnership with Psychmed (part of The Cognition Group), provider of the technology behind the process.

Aim

- A major noise factor in psychiatric clinical trials is likely to be the clinical interview itself by means of which disease severity is to be assessed.[4]
- In order to increase inter-rater reliability, centralized interviews, computerized interviews and statistical monitoring with in-trial rater remediation have been suggested earlier.
  - o A major disadvantage with centralized interviews is exclusion of the role of the Site Rater (SR), who is in direct contact with the patient and caregivers, and who may therefore be in the best position to evaluate the actual clinical status of a patient. Furthermore, language barriers may be difficult to overcome
  - o Disadvantage of statistical monitoring and rater remediation is lack of control on the interview itself.
  - o Disadvantage of computerized interviews is that these may suffer from a similar lack of precision as paper-based, patient self-ratings.
- To overcome these problems, a new methodology and supporting technology have been developed. It allows monitoring of patient interviews and rater bias through remote Independent Rater (IR) feedback. This new method (patent pending), termed Expert Rater Assisted Score Evaluation (ERASE), has been implemented for the first time in a multinational schizophrenia trial. Here we describe the work flow behind ERASE and report on the potential use of this method to enhance signal detection in RCTs.

Technical Set-Up

Hardware and software

Identical notebooks with following features were provided to the sites:

- Dual-core processor (1.66 GHz), 512 MB Ram, 100 GB hard drive (5400 rpm), DVMT
- 1.3 mega-pixel 180° swivel webcam and microphone
- DVD±RW / DVD-Ram optical storage
- Ethernet socket, wireless network adapter

Recording software (running under Windows XP) was pre-installed and accessible through personal, pass-word protected, user accounts. Hard disks were protected from normal access for persons without administrative rights (e.g. investigators).
A toll-free 24/7 Helpdesk service was made accessible for end-user support.

Sites were required to have internet access at a minimum connection speed of 512 Kbs.

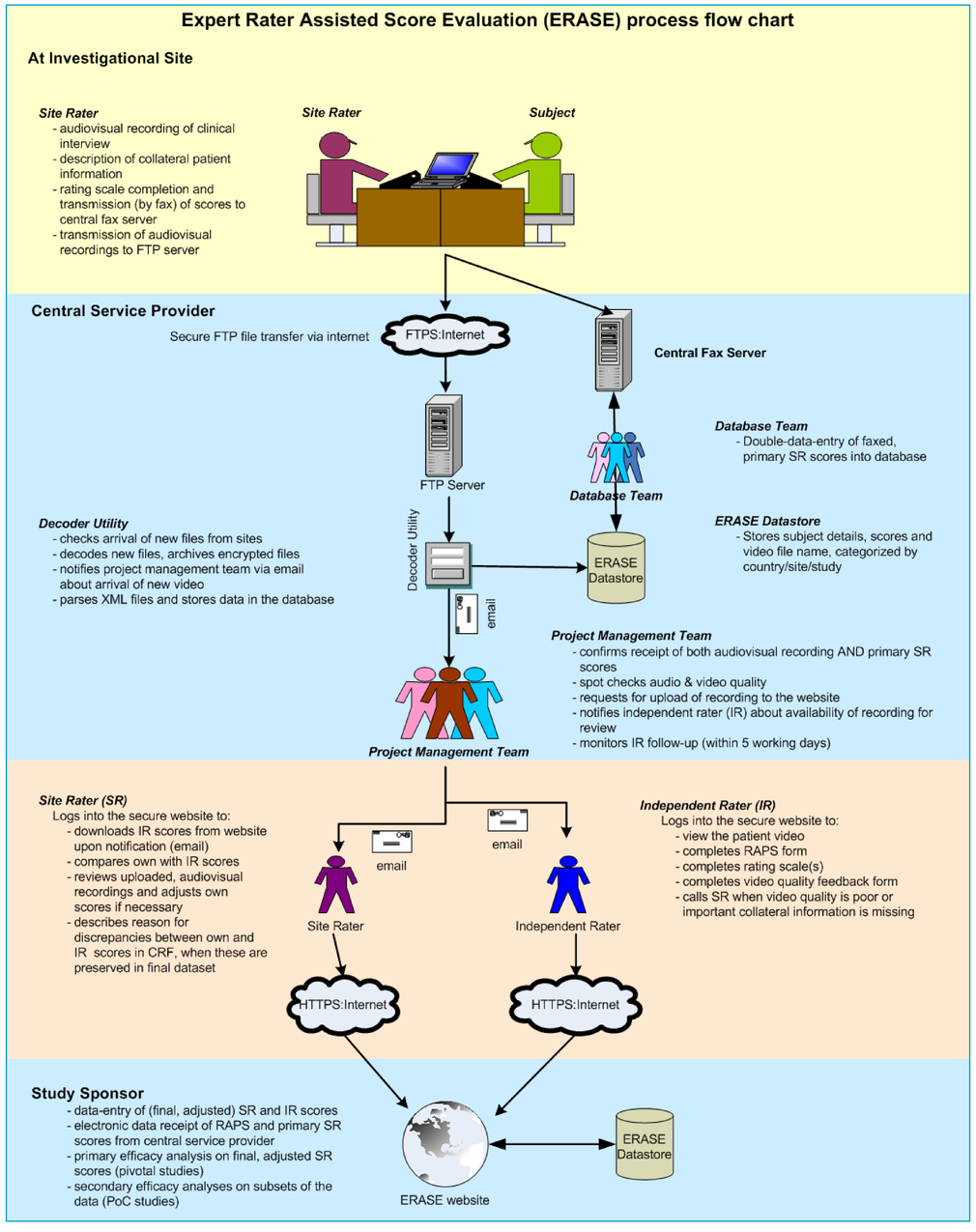

Figure 1.

Study design

- 12 weeks, 3-arm, placebo-controlled, adjunctive treatment of negative symptoms in chronic patients with schizophrenia (n=215)
- 25 Sites in 8 different countries across Europe, Russia and South America
- 126 (Sub-)Investigators
- 15 Independent raters (7 primary + 8 back-up)
- 233 Interviews recorded for PANSS at Screening, and 393 for SANS at Baseline and Endpoint

Results

SR and IR SANS global item scores compared

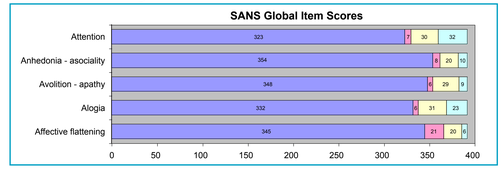

Figure 2. SR SANS global item scores <2 points different from IR scores (blue), missing from IR ratings (red), adjusted (green), or preserved when differing from IR >1 point (yellow).

Acceptability of ERASE in the field

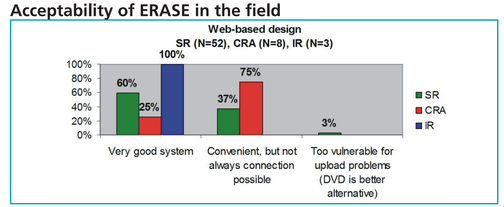

Figure 3. Satisfaction of Site Raters (SR), Independent Raters (IR), and Clinical Research Associates (CRA) with the web-based ERASE system

Technical feasibility of ERASE

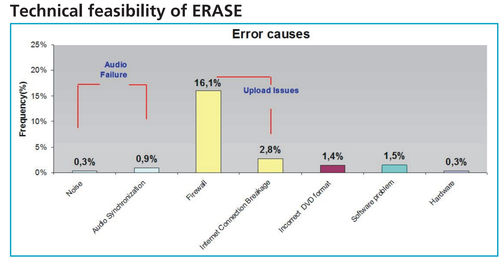

Figure 4. Technical issues encountered during recording or transmission of interviews

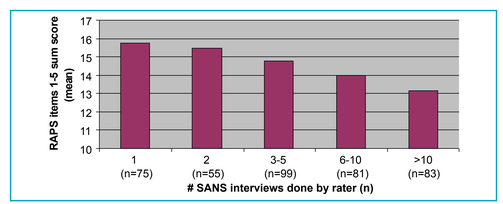

Figure 5. Mean interview quality (RAPS items 1-5 sums score) with growing volume of work

Investigator (enrolment and expectancy) bias

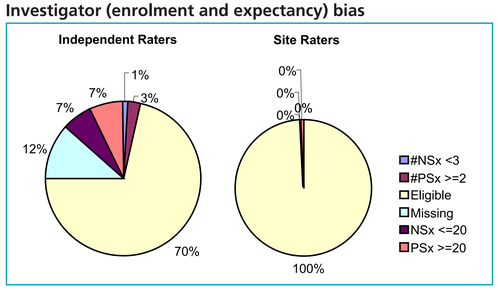

Figure 6. Eligibility based on PANSS scores at Screening (N=214)

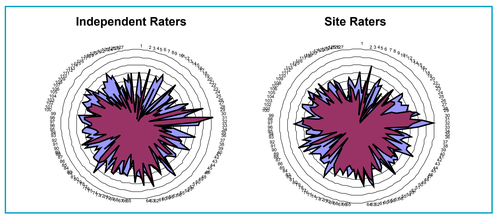

Figure 7. Clinical improvement based on SANS scores at **Baseline** and **Endpoint** (N=127)

Inter-rater reliability

BASELINE + ENDPOINT interviews	# Interviews SR and IR scores Available (N)	Intra-Class Correlation
$SANS_{1-22}$ - composite score	312	0.72
Affective flattening (7)	371	0.59
Alogia (13)	386	0.50
Avolition-apathy (17)	386	0.60
Anhedonia-asociality (22)	384	0.59
Attention (25)	385	0.52

The current dataset will allow the study sponsor to evaluate trial outcome, not only based on the primary efficacy analysis (using the adjusted SR ratings - ITT, LOCF), but also based on high quality subsets of the data, for instance including only subjects:

- Confirmed to be eligible according to IR PANSS scores;
- Interviewed adequately (RAPS score 13-20) at baseline and endpoint;
- With acceptable concordance between SR and IR ratings on SANS.

Conclusions

- **Expert Rater Assisted Score Evaluation (ERASE) is an acceptable and technically feasible, new method that can be used to ensure investigators' adherence to clinical interview and rating guidelines.**
- **ERASE may enhance signal detection (or confirm absence of a clinically relevant effect) in a placebo-controlled RCT when the efficacy analysis involves high quality datasets only.**

References:

1. Kahn A, Kolts R, Rapaport MH, et al. Magnitude of placebo response and drug-placebo differences across psychiatric disorders. Psychological Medicine 2005;35:743-749.
2. Kemp AS, Schooler NR, Kalali AH, et al. What is causing the reduced drug-placebo difference in recent schizophrenia clinical trials and what can be done about it? Schizophrenia Bulletin Advance Access published August 22, 2008.
3. Schoemaker JH, Szegedi A. Factors enhancing placebo response in depression trials. Abstract International Society for CNS Clinical Trials & Methodology (ISCTM) Mid-Year Conference, 17-18 September 2007, Brussels, Belgium.
4. Kobak KA, Feiger AD, Lipsitz JD. Kobak et al (2005). Interview quality and signal detection in clinical trials. American Journal of Psychiatry 162(3):628.

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