

Innovative Technologies Workgroup Notes

September 7, 2019 Meeting, ISCTM Autumn Conference, Copenhagen

14:00-15:30

-Richard Keefe and Mike Davis initiated the workgroup meeting by providing a summary of the workgroup goals and progress thus far. The attendees were then asked to select a small breakout group to join to discuss nomenclature, background, and key issues related to 1) patient recruitment, 2) placebo response, and 3) meaningful change.

Group 1: Timely Recruitment of the Right Patients in Studies (small group leader: Steve Brannan)

Group 2: Placebo Response (small group leaders: Hilda Maibach and Gary Sachs)

Group 3: Measuring Clinically Meaningful Change (small group leaders: Steve Marder, Jana Podhorna)

-After ~45 minutes of small group discussion, the larger workgroup was reconvened. A leader from each small group presented a summary of the small group discussion to the larger workgroup and entertained questions and comments from the larger workgroup.

-At the conclusion of the meeting, representatives from the three small groups were asked to draft a brief document summarizing their discussions. A deadline of 1 month was acceptable to the group representatives.

INDIVIDUAL GROUP NOTES

Group 1: Timely Recruitment of the Right Patients in Studies (small group leader: Steve Brannan)

Our subgroup was tasked with looking at recruitment

- The phrase that we thought captured our goal was *“the timely recruitment of the right patients into studies.”*
- The group began by discussing the various obstacles to achieving our goal.
 - Protocol inclusion and exclusion criteria;
 - if one has too many criteria it slows down recruitment
 - if one is too lax or loose then you do not get the right patients for that study.
 - The group also talked about behavioral psychology and motivations that lead both patients and occasionally sites to either under report or over report symptoms.
 - It was mentioned that investigator behavior may not be conscious.
 - There was a discussion about whether the SCID or the MINI helped identify the right patients (and whether electronic versions might help).
- The group discussed that recruitment times have decreased, and trials are slower
 - Now 0.2 patients per month for a site is not uncommon depending on the indication.
- At least one of our members also is involved with virtual studies, and he mentioned that they can also be slow.
- The group talked briefly about how to attract the right patients, and not just get someone in because “nothing else worked”
 - Subjects in antidepressant and antipsychotic trials can be there because no prior treatment worked
- The group talked a bit about “return of information”, and how to use it
 - to increase subject engagement and attention;
 - also, the role of trial education;
- The group discussed the role of informed consent and technology, how technology is starting to change this;
 - This led to a discussion of patient retention and how that really starts with appropriate consent

Early on we had talked about enrichment strategies for trials including placebo run ins and SPCD, but we never returned to that topic.

Group 2: Placebo Response (small group leaders: Hilda Maibach and Gary Sachs)

What are the opportunities to apply new technologies for placebo response mitigation?

In approaching this question constructively, it is necessary to draw on a nomenclature with defined terms, understand current strategies, and review available literature.

Improving the nomenclature:

I. What is placebo response?

- a. Broad Operational definition: Change measured from pretreatment baseline to end of treatment with an inactive agent.

$$\text{PBO (and Nocebo) response} = X_{\text{baseline}} - X_{\text{final}}$$

Nocebo response (worsening in response to a physiologically inactive intervention) are often apparent at adverse effects.

(For simplicity we will consider Nocebo effects as an instance of placebo response associated with worsening rather than improvement)

This operational definition is problematic since it encompasses several elements with different mechanisms. While each might represent valuable opportunities to improve signal detection, distinguishing between them facilitates the pursuit of innovative remedies.

- b. Parsing Broad Placebo Response into subgroups based on concordance between change in scale and subject's clinical outcomes
 - i. **Scale and subject improve**
 1. -Natural course of illness
 2. -Regression to the mean
 3. -Subjects Responds to treatment received outside protocol
 4. -True placebo Response (improvement due to an active process not initiated by response to a physiologically active drug effect)
 - ii. **Scale improves but subject does not**
 1. -Pseudo-placebo response
 - a. -Poor measurement
 - b. -Intentional mischief

II. Mechanisms associated with "True Placebo Response" (and main proponents)

- a. **Expectation** (Benedetti, Italy)

- i. Baseline beliefs and certainty,
 - 1. Hasni et.al. Pain, 2014
 - ii. Self-efficacy – learned response based on TRT hx,
 - 1. Kessner et.al., PLOS 1, 2014
 - iii. Influenced by Rapport in interaction between Subject and staff
 - iv. Genetic intellectual disability severity inversely correlated with placebo,
 - 1. Curie et.al., PLOS 2017
 - v. More costly drug / labeling more effective,
 - 1. Kan-Hansen STM, 2014
 - vi. Desperate patients or care givers seeking solutions
 - b. **Conditioning** (Manfred Schedlowski, Essen)
 - c. **Other/Ritual** (Ted J. Kaptchuk, Harvard)
 - 1. Rituals reduce anxiety – PD,
 - 2. Benedetti & Carlino, Neuropsychopharma, 2011
 - 3. Karl & Fischer, Hum Nat, 2018
 - 4. Mundt et.al., Ann Behav Med, 2017
 - d.
 - i. Kaptchuk showed the difference between ‘being wait-listed for study’ versus placebo, same in ‘control’ versus 2 active placebo arms,
- III. **Common Current strategies for placebo response mitigation**
 - a. **Predict and restrict**
 - i. Select less placebo responsive subjects
 - ii. Select sites with lower placebo response (or history of separating)
 - b. **Blind and refine (lead-in) Variants**
 - i. Single blind
 - ii. Double blind
 - iii. Multiple baseline
 - iv. Sequential Parallel Comparison Design (SPCD)
 - c. **LOCF (Fix other assumed culprits from last study)**
 - i. Better Scales
 - ii. More stringent response criteria
 - iii. Fewer treatment groups (higher proportion assigned to placebo)
 - iv. Fewer sites/Fewer Subjects
 - v. Increase threshold severity requirement
 - vi. Guard against functional unblinding
 - vii. “Placebo response Training”
 - viii.
- IV. **Technology based solutions to address placebo response**
 - a. Technology can actually contribute to placebo response in various ways
 - i. Websites about studies may provide extensive information about trials to the point that they increase placebo response
 - ii. There are websites that actually instruct subjects on how they should respond to get into clinical trials

- iii. Widespread reporting about clinical trials and new drugs in the media can impact how people view clinical trials
- b. Using training procedures to mitigate placebo response
 - 1.) One of the workgroup participants (I missed his name) described a study that used this approach in the context of patient reported outcome for pain. Specifically, using a diary or experience sampling method. Subjects were required to read instructions intended to minimize placebo response before completing each diary entry. Lower placebo response rates were found relative to rates reported in meta-analyses.

C. Registries

- 2.) It may be useful to set up registries for clinical trials, e.g., to ensure no duplicate subjects are enrolled
- 3.) There are companies that are commonly used in clinical trials to identify individuals attempting to enroll in multiple trials at the same time

D. E-consents

- 4.) May be able to provide study information in a way that minimizes placebo effect (e.g., minimize factors related to human interactions) – present in less biased or leading ways

E. Computer scale administration

- 1.) For clinician rated scales (e.g., MADRAS, PANSS), electronic versions (e.g., tablet based) walk interviews item-by-item through the scale and may help interviewers stick more closely to structured interviews rather than engaging in free-flowing conversation that enhances placebo response associated with human interaction factors
- 2.) Can also be used to monitor for unusual patterns in ratings across assessments (e.g., dramatic improvements)
Blinded data analytics

F. blinded Data Analytics

- 1. High SD has been found in placebo treated subjects vs those receiving active interventions
- 2. Response patterns associated with pbo response

G. Video surveillance with remote quality control

- 3.) This could be used to provide raters feedback to minimize behaviors that enhance placebo response
- 4.) Interviewers typically found to be longer with this approach, but not clear if better

H. Remote assessments with centralized raters

- 5.) This has been used by unclear how successful it has been

I. Virtual reality

- 6.) Might virtual reality based clinical interviews be conducted to standardize the way questions are asked? Could help address human factors that vary across interviewers?
- 7.) VR measures of functioning or functional capacity can provide standardized environments to assess subject functioning than clinical rating scales

J. Objective markers (e.g., physiological or other data from a wearable device) that placebo responses are not possible or placebo groups may not be needed needed?
(NOTE: Not sure I understood this point)

- 8.) For example a pure biomarker of a mediator of response to an active interventions –it might still be necessary to consider placebo response even with such a pure biomarker (and as yet none are known)

Selected References from Placebo Subgroup

1.) Expectancy

- i. Baseline beliefs and certainty,
 1. Hasni et.al. Pain, 2014
- ii. Self-efficacy – learned response based on TRT hx,
 1. Kessner et.al., PLOS 1, 2014
- b. No placebo in severe dementia patients
- c. Genetic intellectual disability severity inversely correlated with placebo,
 - i. Curie et.al., PLOS 2017
- d. More costly drug / labeling more effective,
 - i. Kan-Hansen STM, 2014
- e. Desperate patients or care givers seeking solutions

2.) Rituals

- a. Rituals reduce anxiety – PD,
 - i. Benedetti & Carlino, Neuropsychopharma, 2011
 - ii. Karl & Fischer, Hum Nat, 2018

- b. Kaptchuk showed the difference between 'being wait-listed for study' versus placebo, same in 'control' versus 2 active placebo arms,
 - i. Mundt et.al., Ann Behav Med, 2017

3.) Clinician patient interaction

- a. Ted Kaptchuk -multi-arm placebo trials w significant differences,
 - i. Kaptchuk et.al., -summary of placebo 2013
- b. patient beliefs reinforced by Clinician, allergy RCT,
 - i. Leibowitz Health Psychol, 2019
- c. Placebo or Nocebo – with 'Solicited' Adverse events – baseline tell patients what to expect-'framing'. Then ask if they had (solicit) events. Adverse events in traditional trials are what patient volunteers, soliciting symptoms – is know to bias response
 - i. Dementia & Nocebo, Vredevel, CNS drugs, 2019
- d. Placebo effects in Asthma - children manipulated by clinician interaction,
 - i. Kemeny & Rossenwasser, J Allergy Clin Imm, 2007
- e. Learning appropriate, expected, socially desirable etc response is framed for the attentive and motivated patients and care givers
 - i. Clinician also report placebo response
- f. Placebo response to clinic visit –
 - i. PR-12, Ovchinsky et.al., Otolaryngol Head Neck, 2005
 - ii. Simons et.al., Pain 2014
- g. clinician interview
 - i. Masi et.al., Trans Psych, 2015
 - ii. Superpower glasses stanford – remove clinician effect SRS imp,
 - 1. Daniels, et. al.,NPJ Digital Med 2018

4.) Gender

- a. Pain studies female higher placebo responses,
 - i. Dworkin et.al., Pain, 2010
- b. Females report higher severity higher placebo in IBS,
 - i. Ballou Clin GI Heptol, 2018
- c. Higher subjective effects reported for MA and DA,
 - i. Mayo et.al., Psychopharma, 2019

5.) Type of endpoint- related to Placebo response

- a. objective subjective
 - i. Asthma study – 4 arm – albuterol, placebo inhaler, placebo pill, no treatment After washout FEV 30% improve over Pbo for FEV treadmill test, other 3 arms equivalent. However, self report 'symptom relief' albuterol, placebo pill and Pbo inhaler equivalent, only 'no treatment' arm different on subjective score
- b. Caregiver burden placebo response (untreated children)
 - i. Jones et.al., Autism Research , 2017
- c. Frequency of measurements/periodicity- good bad mood day/
 - i. Recall bias- 'have you been anxious over the past 4 weeks- 'recency'
- d. Low inter-rater reliability,

- 6.) Natural history of disease
 - a. Timing of measures w inter and intra-variability- ebb flow
 - b. MS relapse cycles

- 7.) Regression to the mean
 - a. Screen score inflation – difference from screen to baseline or baseline to visit 1 – largest relative shifts in scores unconscious,
 - i. Kobak, Current Alzheimers Res 2010

 - b. Trial compete for enrollment -so enroll less severe symptoms and younger patients
 - i. Less severe – plays to ‘relative change biases’ shift from zero (0) to one (1) is 100% versus shifts from twenty (20) to ten (10)
 - c. Intra patient variability

- 8.) Patient characteristics
 - a. Placebo modified by genetics
 - i. Genomics in Placebo “placebome” ,
 - 1. Hall et.al. Trends molecular MD 2015,
 - 2. Wang et.al., JCI Insights 2017

 - b. Conscientiousness and anxiety (focused attention)
 - i. Karlington et.al. 2011
 - ii. Specific memory
 - 1. Bartel et.al., Clin Ther 2017

 - c. Top down cognitive skills – Higher IQ – higher Placebo sustained lower
 - i. IQ or plasticity –
 - 1. Ongaro, Pain 2019
 - 2. Tetreault, PLOS bio 2016, brain connectivity 2019
 - ii. Within population – younger patients/children have higher Pbo,
 - 1. Dold, Evid based Med 2015
 - 2. Kroon Van Diest, Curr Pain Headache 2017

 - d. Depressive, Catastrophising inverse to response, optimism better placebo, smaller nocebo; more sympathetic/ less disruptive ASD lower placebo
 - i. Geers et.al., J Psychosom Res, 2007
 - ii. Morton et.,al., Pain, 2009
 - iii. King et.al., JAMA Pediatr 2013
 - e. Attention seeking and ‘enjoyment’ higher placebo,
 - i. Scott et. al., Arch Gen Psych 2008
 - f. Placebo response similar pathways as learning – fMRI studies,

Rutherford and Roose

TABLE 2. Study Design Features Influencing Placebo Response in Antidepressant Clinical Trials

Increase Placebo Response	Decrease Placebo Response	Strength of Evidence
More study sites	Fewer study sites	Strong
Poor rater blinding	Good rater blinding with blind assessment	Strong
Multiple active treatment arms	Single active treatment arm	Strong
Lower probability of receiving placebo	Higher probability of receiving placebo	Strong
Single baseline rating	Multiple baseline ratings	Medium
Briefer duration of illness in current episode	Longer duration of illness in current episode	Medium
More study visits	Fewer study visits	Medium
Sample of symptomatic volunteers	Sample of self-referred patients	Weak
Optimistic/enthusiastic clinicians	Pessimistic/neutral clinicians	Weak

Group 3: Measuring Clinically Meaningful Change (small group leaders: Steve Marder, Jana Podharna)

The group focused on the challenges in characterizing meaningful change in studies using new technologies. We addressed whether new technologies can help to define meaningful change? We discussed the advantage of using new technology: Real-life capture (objective) versus observations by somebody else (subjective)

1. Among the challenges is whether meaningful change should be defined by effect size on a scale, change that is meaningful for a patient, or change using health economic measures.
2. Considerable discussion was devoted to determining what is valued by an individual patient. Some may be interested in independent living or walking a dog whereas others may be interested in work or school. How can a measure of meaningful change incorporate these very different endpoints.
3. Another challenge is how to deal with the very large data sets that will emerge from studies using passive monitoring.
4. There was concern about defining the right time of collecting and the minimum time to expect change. Change in social behaviors may require monitoring relatively lengthy periods.
5. Understanding complex behaviors may require looking at behavior patterns rather than a particular endpoint.
6. There was concern about the sensitivity to detect change with new technologies. Also, is normative data important for understanding certain behaviors as measured by digital technology?
7. There was a discussion as to the usefulness of focusing on a discrete timepoint versus looking at continuous change. Studies using new technology will need to study the variability of what is being measured.
8. How innovative technologies can help measure what current scales fail to detect (e.g., social behavior), aware of cultural difference & what would be 'normal' or norms?
9. There was considerable discussion of the ability to collect large amounts of data versus making sense out of it
10. There was concern about strategies for measuring occasional events that have substantial importance.
11. The group agreed on the advantages of real-life monitoring vs. rater-based questionnaires