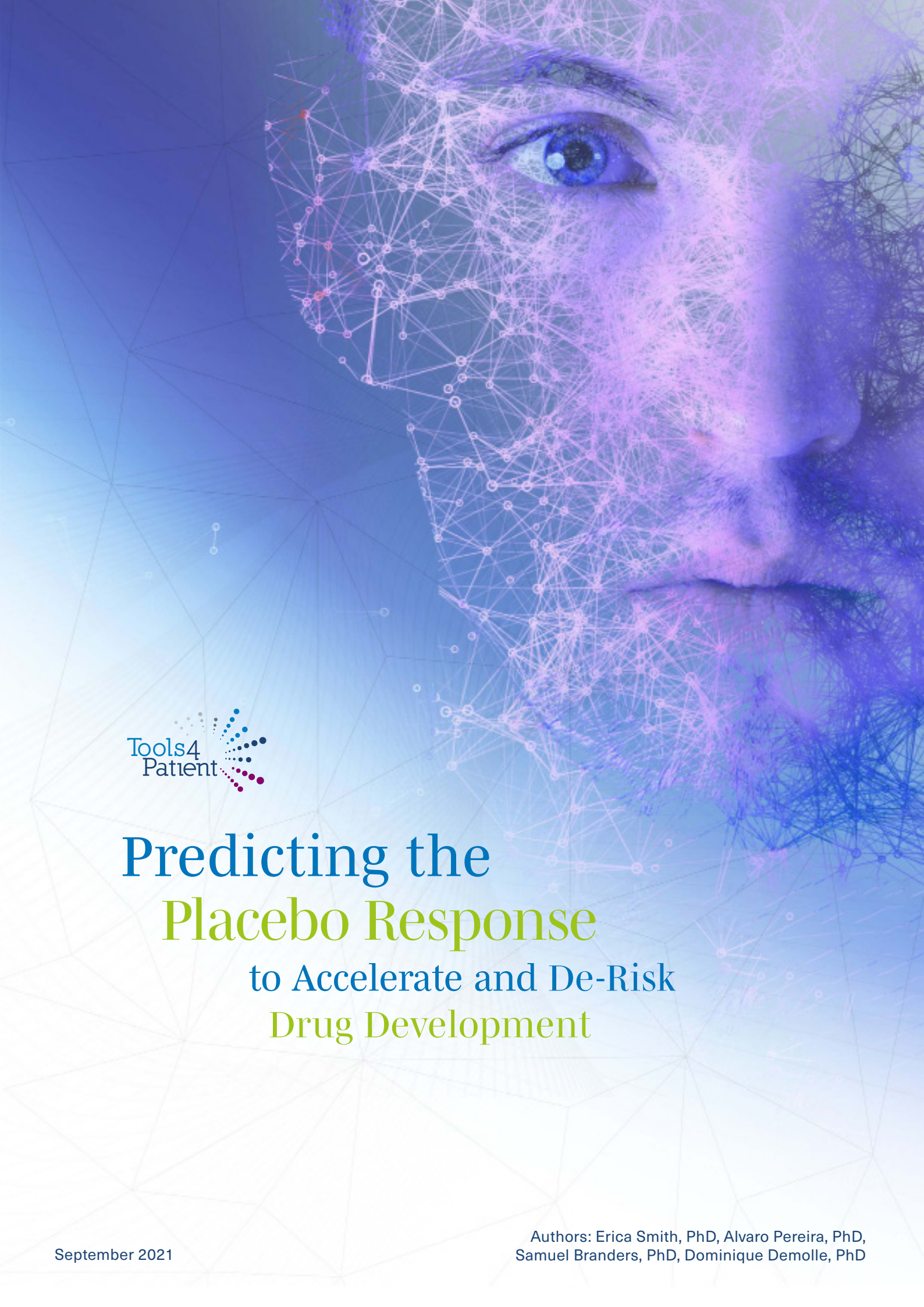

Tools4 Patient

Predicting the Placebo Response to Accelerate and De-Risk Drug Development

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The influence of patient psychology on response to treatment and placebo can no longer be ignored. Tools4Patient (T4P) provides proven solutions that use insights from clinical trial patient psychology to improve drug development. T4P works with the most innovative pharma and biotech companies, CROs and KOLs to apply AI-powered algorithms based on a quantitative understanding of patient psychological traits, perceptions and beliefs that predict patient behavior and treatment response in clinical trials. Led by scientific key opinion leaders, T4P technologies allow sponsors to account for the inherent differences between patients and to benefit from this critical information when analyzing clinical trial data. T4P's flagship technology, Placebell©™, predicts placebo response – a major source of clinical trial failures – in trial patients and results in substantial increase in clinical trial success rate with no risk to data analysis or study conduct. By using AI to address the placebo response paired with time-tested approaches for statistical data analysis, Placebell©™ reduces drug development risk, timelines and cost. Using Placebell©™ and other T4P solutions focusing on patient compliance or site-based data variation provides actionable insights to sponsors that empower decision-making and illuminate the path forward in drug development.

Intelligent drugs need intelligent data.

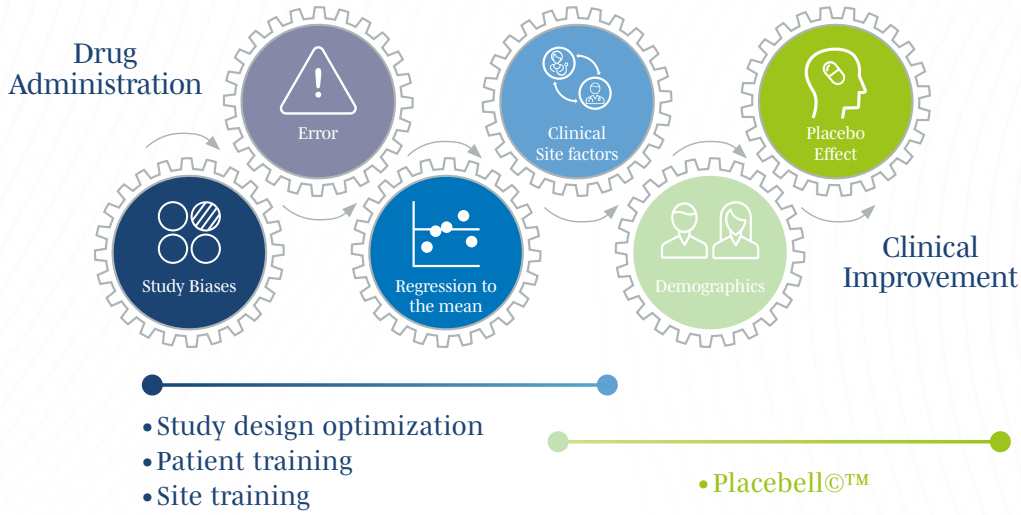
The challenge of the placebo effect in Phase II and Phase III clinical trials

The average cost of drug development was estimated at $2.6 billion in 2016, having increased at an annual rate of 8.5% above general price inflation[1]. This high cost is associated with low success rates, particularly of drugs entering clinical development – which was recently estimated to be 13.8%[2], noting that drugs targeting central nervous system conditions have some of the lowest success rates[3]. The high cost, long development timelines and intense risk involved in developing new drugs is a significant barrier to providing needed therapies to patients and has been the impetus behind the development of unique strategies to de-risk the drug development process.

Phase II and III clinical trials fail due to safety issues or the inability to demostrate clear superiority of the tested therapy versus a placebo, which can lead to increased development costs, extended timelines and even the premature abandonment of entire development programs[4,5]. Designing clinical trials to definitively demonstrate efficacy and safety of an experimental therapeutic requires a sophisticated understanding of multiple factors, including disease progression, appropriate endpoints, variability in patient response to treatment and the potential for a strong placebo response in a specific disease or population. Regardless of the size and therapeutic area of a Phase II or III clinical trial, the placebo effect creates a very real challenge that must be understood and managed. For example, in an evaluation of 83 Phase 3 trials across therapeutic areas that were conducted and/or submitted between 2007 and 2010, 32% of trials failed to demonstrate a statistically significant difference of drug effect against placebo[6].

By nature, the placebo response is a complex psychobiological phenomenon with significant psychosocial components that include treatment environment, individual patient and clinician factors, and the interactions among them[8–11] (Figure 1). Behavioral, psychophysiological, and neuroimaging studies have shown that the placebo effect is associated with changes in biochemical pathways in the brain[12–15]. The placebo effect is inherently patient-specific, influenced by the investigator's behavior toward his/her patient, the patient's expectations (in terms of drug efficacy and overall well-being), and certain well-defined personality traits[8,16–20]. Consequently, the patient-specific nature of the placebo effect may introduce a bias and/or variability in randomized clinical trials.

Figure 1



Multiple factors contribute to the individual placebo response in clinical trials, including biases in study design, errors in patient reporting of symptoms, regression to the mean, and the true placebo effect that relates to the individual patient's psychology and biology. Historical methods like training of patients and sites focus on different aspects of the placebo response than the novel Placebell©™ approach.

Historical methods to manage the placebo response

The first attempt to manage the placebo effect was to reduce placebo response by improving study designs when conducting randomized clinical trials (RCTs). For example, studies may incorporate a placebo run-in phase (or lead-in phase) design, in which patients showing an improvement upon administration of placebo were excluded from the study. A variant of the placebo run-in phase design is the sequential parallel comparison design involving two double blind identical steps[21]. These approaches, however, have failed to yield the expected impact on trial sensitivity. Meta-analysis in antidepressant RCTs demonstrated that placebo lead-in phases did not decrease the placebo response, nor increase the difference in response between active drug and placebo groups[22,23]. In fact, use of a Sequential Parallel Comparison Design (SPCD) was cited as a potential reason for rejection of a recent application of a drug to treat depression[24].

IMMPACT (Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials)[25] consortium examined several areas to increase outcome measurement sensitivity in chronic pain studies: patient psychology, expectations, investigator site training and staff-patient interactions.

As an alternative to improving study sensitivity by trial design only, the IMMPACT (Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials)[25] consortium examined several additional areas to increase outcome measurement sensitivity in chronic pain studies: patient psychology, expectations, investigator site training and staff-patient interactions. The consortium suggested taking some or all these factors into account when conducting a chronic pain control study[25].

In pain trials, training of patients to report pain symptoms more accurately and reproducibly is commonly performed – although literature reports on the actual reduction in data variability produced by patient training and its impact on efficacy evaluation are scarce. For example, in one recent study, training of both patients and staff resulted in a decrease in the proportion of high placebo responders (defined as placebo-treated patients with greater than 30% reduction in average pain score compared to baseline) in a chronic low back pain trail compared to literature reports[26] In other recent literature, however, patient training did not result in improved ability to detect the efficacy of pregabalin in a randomized controlled trial[27].

The recommendations made by the IMMPACT group can be generalized to include indications other than pain. For example, in schizophrenia, using only clinical raters that have high intraclass correlation (i.e. high level of agreement with other raters in the study) reduces data variability[28]. In depression, new clinical trial statistical approaches have been suggested to improve the 'true' treatment effect evaluation using nonlinear longitudinal modelling of clinical scores. However, in this method, high placebo responders were excluded after post-hoc analysis, which limits the ability to generalize the data to a more heterogeneous real-world patient population[29].

While the field has been struggling to limit the impact of the placebo response in drug development in a variety of diseases, one universal solution has not yet been found. Optimizing study designs may be helpful but may also be a significant source of study bias and have been met with regulatory resistance. Patient and investigator site training has been widely employed in pain trials, although they can be challenging to implement in large, multi-center trials. It is also far more difficult to train patients to more accurately report symptoms that are highly complex and less intuitive than pain (e.g. Quality of Life scales). Furthermore, none of these methods incorporate two of the main factors put forth by the IMMPACT group: patient personality and expectation. Until now, there have been no existing methods that fully address the variance attributed to the placebo effect as a true psychobiological phenomenon.

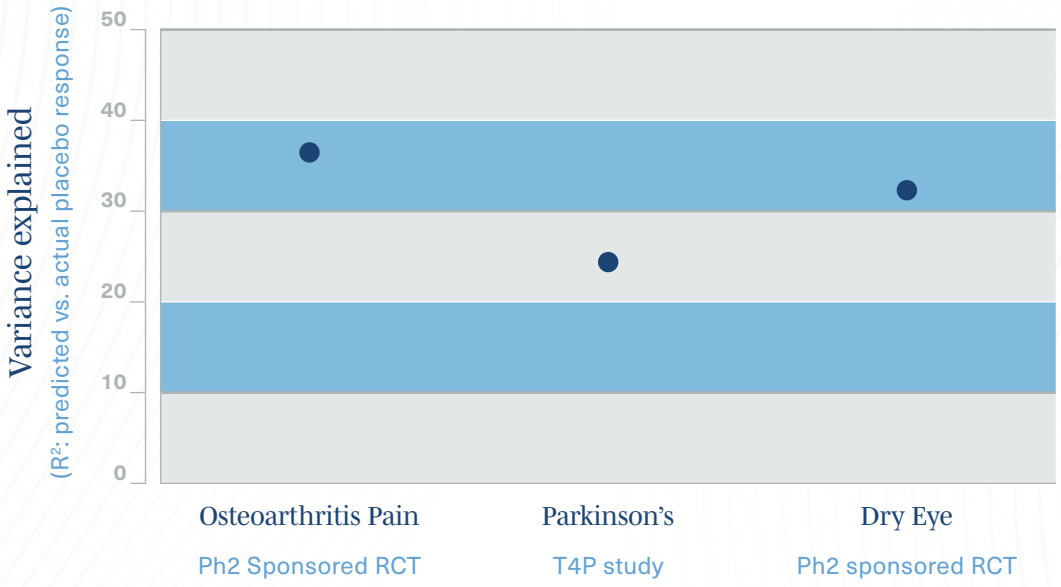
The Placebell©™ Covariate approach

The decades of research on the placebo response emphasize the importance of considering the unique characteristics of each patient – including personality – to evaluate the potential for a high placebo response based on the strong relationship reported in the literature[19, 30–32]. There has, however been an obvious gap between scientific understanding and approaches that have applicability in an industrial clinical trial setting. This paper describes a unique approach –Placebell©™ – that uses predictive algorithms to define individual patient placebo responsiveness at baseline based on patient psychology, expectation and other factors (e.g. age, demographics, baseline disease intensity).

The Placebell©™ approach is intended to robustly predict the range of placebo responsiveness in clinical trial participants with minimal trial burden and absolutely no additional study risk. Placebell©™ models can be calibrated specifically in each disease using a proprietary machine-learning based algorithm to select and weight multiple features related to the placebo response.

This model is then used to calculate a single score, the Placebell©™ Covariate, for each patient in the study. When used in the statistical analysis, the Placebell©™ Covariate can dramatically reduce data variance, thus reduce data variance, improving the ability to detect true treatment efficacy. Furthermore, the Placebell©™ approach is complementary to other methods that may be used to attempt to minimize the placebo response (e.g. patient training, site training) as these address different components of the placebo response.

Figure 2



Placebell©™ has been applied in different therapeutic areas, including pain, neurology (Parkinson's disease) and Ophthalmology (dry eye disease) and has achieved similar explanation of variance.

Placebell©™ models have been constructed in multiple diseases, with more than 10 clinical studies completed. Model performance has been consistent in chronic pain, Parkinson's disease and ophthalmology (dry eye disease) (Figure 2), with additional studies ongoing in areas like psychiatry, auto-immune disease and inflammation. In general, Placebell©™ has been demonstrated to explain between 25-35% of data variability related to the placebo response across endpoints and indications, regardless of route of drug administration and study context (e.g. conventional in-person trial versus virtual trial).

Figure 3

How Placebell©™ Works

Placebell©™ is simple to implement in only 3 steps:

Step 1:

Assess Patient Psychology

Step 2:

Predict each Patient's Placebo Responsiveness

Step 3:

Provide all Patients' Placebell©™ Scores to Study Statisticians

Placebell©™ can easily be implemented in three steps: (1) assess patient psychology using the Multi-Dimensional Psychological Questionnaire (MPsQ), (2) predict each patient's placebo responsiveness using our proprietary machine learning-based models to calculate each patient's Placebell©™; (3) provide all patients' Placebell©™ scores to study statisticians to use as a covariate in statistical analyses. This approach can be incorporated into any clinical trial regardless of size, design or context (e.g. in-person trials vs. decentralized or virtual trials) and is an efficient way to improve study power and reduce the risk of trial failure.

1. **Assess each patient's psychological traits using Tools4Pateint's proprietary MPsQ questionnaire.**

   The Multi-Dimensional Psychological Questionnaire (MPsQ) has been developed by Tools4Patient specifically to assess psychological traits related to the placebo response in clinical trial patients. This questionnaire is divided into 4 separate modules that evaluate psychological traits, patient expectation for improvement, the patient's perception of clinical trial contextual factors (e.g. relationship with the clinical site staff, impression of clinical site surroundings, etc.) and motivation for participating in the trial. As the MPsQ evaluates stable psychological traits, it has been shown to be highly repeatable over time when given to patients as much as 3 years after the initial administration (Chronbach's alpha > 80%). The timing of MPsQ module administration can be customized for each study to maximize the scientific value while minimizing patient burden at any specific study visit, noting that all data must be collected before the first administration of drug as it is used in the calculation of a baseline covariate.

2. **Predict each patient's placebo responsiveness.**

   Once the MPsQ data is collected, it is combined with other standard data collected at baseline (e.g. demographics, medical history, baseline disease intensity) and used as inputs to the disease-specific Placebell©™ model that has been

Regulatory Guidelines for Use of Baseline Covariates

Baseline covariates are used in over **80%** of clinical trials[33] to account for sources of data variability that may or may not be related to treatment response. Because they are so widely used, the practical utility of baseline covariates has been in regulatory guidances issued by the FDA and EMA. The **"Guideline on Adjustment for baseline covariates in clinical trials"** published by the **EMA** became effective as of 01 September 2015[34]. The FDA issued **"Adjusting for Covariates in Randomized Clinical Trials for Drugs and Biologics with Continuous Outcomes: Guidance for Industry"**[35] was put forth in draft form in April 2019 and updated in May 2021.

built using machine learning. This results in the calculation of a single score, on a continuous scale, that relates to each patient's predicted placebo responsiveness. This essentially ranks all trial patients based on placebo responsiveness.

3. **Provide Placebell©™ Covariate to study statisticians.**

The Placebell©™ Covariate score is then given to study statisticians to include in the ANCOVA used to compare experimental groups and determine if differences are statistically meaningful. Covariates in general are an efficient way to account for inherent, baseline differences between patients (e.g. age, gender, etc.) that can increase data variability. Adjusting for these inherent patient characteristics reduces the related data variability and improves the likelihood of detecting statistically significant differences between study groups. Similarly, using the Placebell©™ Covariate allows study statisticians to adjust for the range of innate placebo responsiveness between patients as a major factor that contributes to data variability in both placebo-treated and drug-treated patients. As with any covariate, the Placebell©™ Covariate reduces data variability, increases study power and has the potential to improve p-values.

The EMA and FDA Guidances define the use of covariates in statistical analyses

Analysis of Covariance (ANCOVA) can be used to adjust for differences between treatment groups in relevant baseline variables to improve power and improve estimates of treatment effect.

Covariates must be measured before randomization.

Covariates selected should be prospectively specified in the protocol or statistical analysis plan.

Stratification can be used to ensure balance of treatment across covariates; in this case, these factors should also be used as covariates

The number of covariates should be minimized when possible

Building a Placebell©™ Model

Placebell©™ models are built – or calibrated – for each specific disease / indication to maximize the amount of variance that can be explained (and thus reduced) in the statistical analysis. To build a Placebell©™ model in a new disease, the relevant features – or model inputs – must first be selected. These features may include psychological traits or facets (measured by the MPsQ), disease intensity at baseline, demographics or certain disease-specific characteristics (e.g. duration of disease). While the important features are proposed a priori, machine learning techniques like Recursive Feature Elimination (RFE) are used to confirm the relevance of these features. The weights of these selected features are then learned using Gaussian Processes with a linear kernel (Ridge regression) using data from placebo-treated patients, and model performance is estimated using repeated random sub-sampling techniques (e,g. Monte Carlo Cross-Validation). This process produces a Placebell©™ model whose features and weights are uniquely tuned for the specific indication of interest that can be pre-specified before the start of a clinical trial and thus be used in the calculation of a baseline covariate. This model continually learns using data from subsequent clinical trials.

The potential to de-risk and accelerate clinical drug development

Results

Chronic Pain

The Placebell©™ chronic pain model has been trained using data from N=211 patients from several clinical studies conducted by Tools4Patient. These studies evaluated pain outcomes in chronic pain patients with either peripheral neuropathic pain (PNP) or painful osteoarthritis (OA) of the hip and/or knee receiving oral placebo BID. This chronic pain model was fully pre-specified in the statistical analysis plan of a sponsored Phase 2 randomized clinical trial evaluating a single dose of an experimental therapy administered by intra-articular injection in patients with moderate to severe painful knee OA (NCT04129944) and was used to calculate the Placebell©™ Covariate score for both placebo-treated and drug-treated patients.

Table 1

	Placebo-treated patients					All Patients				
	Pearson's Correlation (predicted vs. actual)					Pearson's Correlation (predicted vs. actual)				
	N	Estimate	95% CI	P-Value	R^2	N	Estimate	95% CI	P-Value	R^2
APS	41	45.8%	[17.5, 67.1]	0.003	21.0%	170	39.9%	[26.4, 51.8]	<0.001	15.9%
WOMAC-Pain	42	59.7%	[35.7, 76.2]	<0.001	35.6%	173	52.6%	[40.9, 62.6]	<0.001	27.7%
WOMAC-Phys	42	57.1%	[32.3, 74.5]	<0.001	32.6%	173	47.1%	[34.6, 58.0]	<0.001	22.2%
WOMAC-Stiffs	42	55.2%	[29.8, 73.3]	<0.001	30.4%	173	55.4%	[44.1, 64.9]	<0.001	30.7%
PGA	42	55.0%	[29.5, 73.1]	<0.001	30.2%	173	49.2%	[37.0, 59.7]	<0.001	24.2%

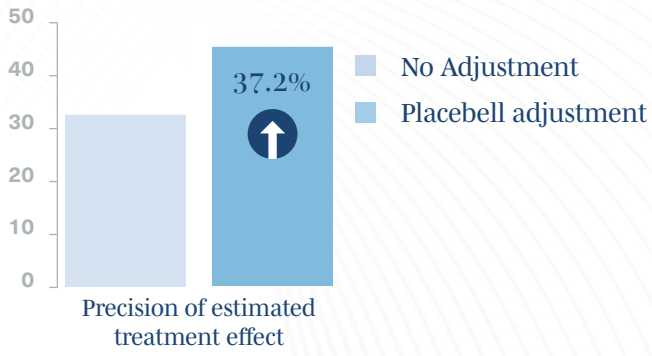
R^2 = Magnitude of variance reduction in statistical analysis

The Placebell©™ chronic pain model was trained from previous T4P-sponsored clinical trials in PNP and OA and was pre-specified in a Phase 2 randomized controlled trial conducted by a biotech sponsor. Results demonstrated that Placebell©™ significantly predicted placebo response based on multiple endpoints in placebo-treated patients (p<0.001 for most endpoints), resulting in reduction in data variability of 21-36%.

The performance of the model was determined by comparing the Placebell©™ Covariate score (predicted placebo response) with the actual placebo response in placebo-treated patients for multiple study endpoints (average pain score (APS), WOMAC-Pain, WOMAC-physical function, WOMAC-stiffness, patient global assessment (PGA)). The Placebell©™ prediction of placebo response was significant, with a Pearson's correlation ranging from 55.2% to 59.7% for the 3 components of the WOMAC battery (R^2 ranging from 30.4% to 35.6%, $p<0.001$)[36] (Table 1).

The Placebell©™ model was further predictive for all patients in the trial (R^2 ranging from 15.9% to 30.7%, $p<0.001$). The R^2 value relates to the magnitude of variance that can be reduced when this score is used as a baseline covariate in the ANCOVA. As such, using Placebell©™ as a covariate results in a substantial decrease in data variability that translates into a 37.2% improvement in the precision of the treatment effect estimation, demonstrating that this tool effectively increases clinical trial assay sensitivity (Figure 4).

Figure 4



Using Placebell©™ in a Phase 2 randomized controlled trial conducted by a biotech sponsor resulted in a more precise estimation of the treatment effect. This indicates that Placebell©™ improved the "assay sensitivity", or the ability to distinguish treatment response from placebo response, in this clinical trial.

Parkinson's Disease

Predictive covariates of the placebo response in Parkinson's disease were built and trained using data from N=94 patients with mild to moderate Parkinson's disease receiving placebo orally by blinded administration (TID) for 3 months in a clinical study conducted by Tools4Patient. The placebo response in this study was assessed as change from baseline in MDS-UPDRS parts 1, II, III and IV, Investigatory Global Assessment of Change (IGAC), Patient Global Assessment of Change (PGAC), Parkinson's Disease Questionnaire (PDQ-39), Epworth Sleep Scale (ESS) and Fatigue Severity Scale (FSS). While the placebo response in MDS-UPDRS Part III (primary endpoint) was small in this study, a predictive Placebell©™ model was still able to be trained using these data.

The performance of the model was determined by comparing the Placebell©™ Covariate score (predicted placebo response) with the actual placebo response for all study endpoints. A multivariate descriptive analysis was used to estimate the predictivity of the placebo response. This analysis demonstrated that Placebell©™ significantly predicted the placebo response in MDS-UPDRS Part III, Part II and Part IV, PDQ-39, ESS, IGAC and PGAC with adjusted R^2 values ranging from 0.16 to 0.33[37] (Table 2). This study defines a Placebell©™ model that can be fully pre-specified in sponsored RCTs to reduce variability and increase study power.

Table 2

Pearson's Correlation: predicted vs. actual placebo response			
	N	R^2	P-value
MDS-UPDRS-3 (primary endpoint)	94	33.2%	<0.001
MDS-UPDRS-1	93	11.0%	0.084
MDS-UPDRS-2	94	14.5%	0.037
MDS-UPDRS-4	88	22.4%	0.007
PDQ-39	94	23.2%	0.003
FSS	92	11.4%	0.078
ESS	93	15.7%	0.029
IGAC	84	43.1%	<0.001
PGAC	94	43.4%	<0.001

R^2 = Magnitude of variance reduction in statistical analysis

A Placebell©™ model was trained in Parkinson's disease using data from placebo-treated patients, and performance was estimated by cross-validation. The prediction was significant for most endpoints examined. The correlation between predicted and actual placebo response – and the amount of variance that can be reduced in statistical data analysis – was substantial, with an R^2 value ranging between 11 and 43%.

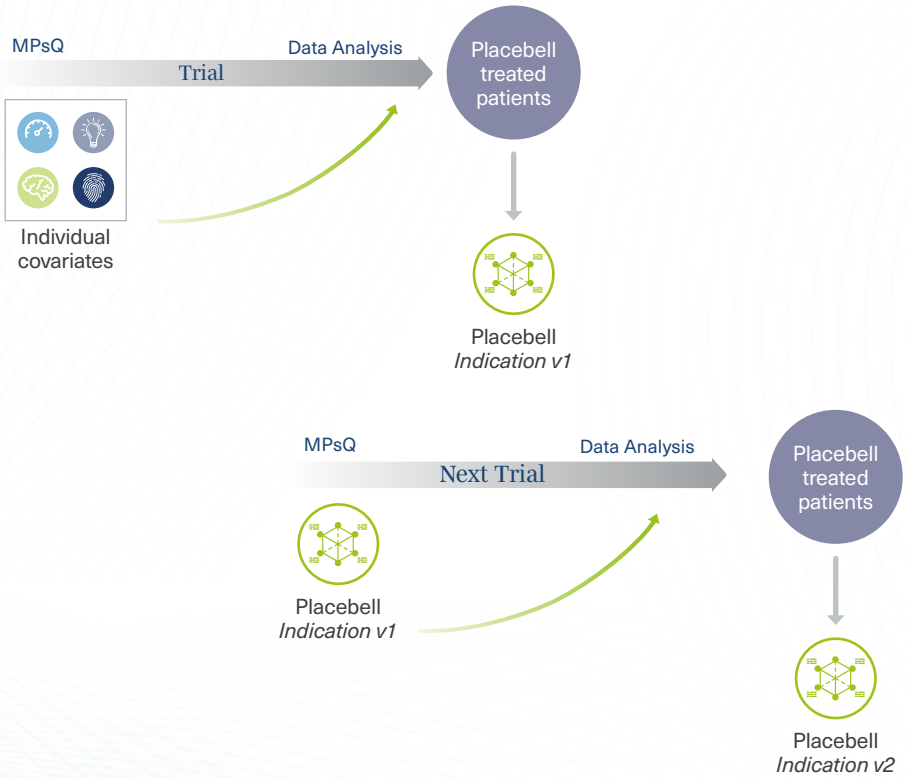
Dry Eye Disease

Data from a phase 2 randomized controlled trial run by a biotech sponsor were used to calibrate Placebell©™ in dry eye disease. In this study, a multivariate analysis was conducted to address multiple sources of data variability unrelated to the treatment response (e.g. placebo response, variability between patient types, variability between clinical sites) for two subjective endpoints: eye dryness score (EDS) and ocular discomfort score (ODS). The R^2 describing the correlation between predicted and actual placebo response in this study was 25-28% ($p<0.001$). Applying the Placebell©™ approach to the analysis of data in this study enabled the sponsor to rule out several major sources of bias in the results and gain confidence that differences between groups were related to the experimental treatment.

Applying Placebell©™ in new diseases

The Placebell©™ model is ideally re-calibrated – or "tuned" – in each specific disease area to maximize the predictive performance for that indication. Disease-specific Placebell©™ models have been or are being calibrated in pain, neurology (Parkinson's disease), psychiatry (schizophrenia), Ophthalmology (dry eye disease), inflammation, immunology and more.

Figure 5



Schematic representing approach to calibrate Placebell©™ in new disease while still benefitting initial trials. In this paradigm, either Individual covariates derived from important psychological features and/or theoretical predictive models can be pre-specified in the statistical analysis of the first trial in the new indication. The data from placebo-treated patients in this first trial will then be used to train the Placebell©™ model in the new disease, which can then be pre-specified in any subsequent trials.

There are, however, options to apply the Placebell©™ approach even in indications in which a fully defined Placebell©™ model is not yet available. In these situations, two approaches can be considered for the first trial in the new indication, and the Placebell©™ model can then be calibrated using placebo-treated patients from this trial:

- Individual covariates related to psychological characteristics that are important features in all Placebell©™ analyses to date can be pre-specified in the statistical analysis. The only requirement for this approach is that the MPsQ is included in the study.

- A theoretical model can be applied based on meta-analysis of previous studies in single or multiple indications.

These approaches are intended to provide immediate benefit to program regardless of Placebell©™ development status. While the magnitude of variance explained in this paradigm may be less than with the fully-trained Placebell©™ model, importantly, adding these covariates to the statistical analysis poses absolutely no risk and can only benefit the trial.

As Placebell©™ is powered by machine learning, models are continually learning as new data are included in analyses – so even fully-trained models will continue to improve over time.

The Placebell©™ method

significantly and repeatedly

predicts placebo response

Discussion

Placebell©™ poses no risk to data analyses yet substantially increases the probability of trial success.

Using the Placebell©™ Covariate score as a baseline covariate in an ANCOVA is an inherently conservative approach with a minimal risk profile. Baseline covariates are widely used in analysis of clinical trial data to remove bias resulting from confounding factors (e.g. age, gender, BMI, etc.) and follow the EMA Guidance[34] and draft FDA Guidance[35]. By definition, a covariate will only decrease the risk of type II error (false negative) without an associate risk of a type 1 error (false positive). Furthermore, there is no potential for a covariate to harm the data analysis so there is no risk to the sponsor when including Placebell©™ in a study. Lastly, the Placebell©™ Covariate is a composite covariate that combines data from multiple patient features defined at baseline into a single score. As such, the resulting statistical analysis only loses one degree of freedom – or the equivalent of one patient in the study. As such, a baseline covariate approach is a low-risk, conservative method to reducing the impact of the placebo response on clinical data.

This low risk profile is associated with a tremendous positive impact on study power and/or required sample size of the clinical trial based on the observed ~30% reduction in data variability related to the placebo response in indications evaluated to date. To illustrate this concept, one can consider a clinical trial with N=100 patients that is powered to 80% (Figure 6). Reduction in variance by 30% translates into increasing study power from 80% to 92% - meaning that the risk

of trial failure due to false negative results is dramatically decreased. Looking at this another way, the trial now has an equivalent power to a trial that included 43% more patients. Conversely, this same study now only requires 70 patients to achieve a power of 80%. Over time, use of the Placebell©™ Covariate could result in reduced sample size in clinical trials, which quickly translates to reduction in clinical trial costs and timelines, and quicker delivery of drugs to market

Figure 6

Change in Variance	Equivalent Sample Size at 80%	Power With 100 Subjects	Sample Size to Reach Power of 80%
0%	100	80%	100
-10%	110	84%	90
-20%	120	88%	80
-30%	143	92%	70

Reducing data variability by 30% with Placebell©™ translates into a substantial increase in study power, or a reduction in number of patients needed to achieve 80% power.

Utilizing the Placebell©™ Covariate to improve study power, p-values and estimation of true treatment effect is both a powerful and conservative approach, yet these data can also be used in other ways in the drug development process. The Placebell©™ Covariate can also be used during randomization to ensure a balance of placebo responders and non-responders in study groups, using a method that has been previously described[38]. This may be particularly relevant for small studies and/or studies early in the development process. Alternately, the Placebell©™ Covariate could be used for patient selection (i.e. to preferentially exclude high placebo responders from clinical trials). This strategy should be carefully considered as it may also limit the extent to which the data could be applied to a generalized population and may not be appropriate for all clinical studies or programs. Alternately, using the Placebell©™ Covariate to adjust for some of the placebo response-related variability

in a study may thus allow placebo responders to remain in the trial while limiting the risk of compromising the study analysis.

The Placebell©™ method represents a unique opportunity to limit the impact of the placebo response in drug development beyond historically or currently available methods. Current methods involve reducing "noise" related to errors in reporting of patient-reported outcomes or minimizing the influence of clinical investigator or site staff on the study outcome, while Placebell©™ predicts placebo responsiveness a priori based on baseline patient characteristics and personality traits. Considering that these methods are non-overlapping, all these tools are complementary and can be used in a single trial. Compared to extensive training protocols that are administered to clinical trial patients and site staff, the Placebell©™ method involves only a single administration of the MPsQ questionnaire and thus adds minimal burden to even the most complex trial.

While the data presented here are focused chronic pain and Parkinson's disease, the Placebell©™ method can easily be applied to any disease or therapeutic area in which the placebo response poses a major challenge to evaluation of true therapeutic efficacy. For example, the Placebell©™ approach has clear application in neurological and psychiatric indications, as well as areas like ophthalmology,

The Placebell©™ approach represents several steps forward in the scientific understanding of the placebo response and its management in drug development.

1

This platform addresses patient psychology and expectation in a systematic and quantitative manner;

2

This platform allows investigators to begin considering the placebo response on an individual patient basis, and not only as a group phenomenon. As such, using the Placebell©™ approach offers a unique opportunity to understand the impact of the placebo response in drug-treated patients as well as placebo-treated patients;

3

The Placebell©™ platform can be re-tuned or calibrated for different diseases to generate a model that has specific maximum predictive power. Generation of these disease-specific models will provide insight into the bases of the placebo response that are common between diseases, as well as the components that are unique to specific indications.

dermatology, and musculoskeletal, genitourinary and gastrointestinal diseases. The Placebell©™ method can also applied to virtually any study design, and is scalable to large, industrial clinical trials that may likely run at dozens of sites in varied geographies. sites in varied geographies.

Conclusion

Effectively improve assay sensitivity in chronic pain, Parkinson's disease ophthalmology and beyond

The Placebell©™ method is a novel, innovative solution to the challenges that the placebo response creates in the drug development process. This approach is robust, powerful and easily adapted to different diseases, study designs and trial logistics. Placebell©™ has been shown to effectively improve assay sensitivity in chronic pain and Parkinson's disease, and has applicability in essentially all therapeutic areas. When used in early phases of clinical development, the increased statistical power could improve decision making and provide greater confidence in identifying the true superiority of active compounds versus placebo. Less effective compounds could be eliminated earlier reducing the number of molecules that fail to demonstrate efficacy in Phase 3. When used in later phases of clinical development, the increased study power reduces the risk of trial failure, which can be catastrophic to drug development programs and companies. Furthermore, this approach corrects for the placebo response rather than excluding placebo responders in clinical trials. The Placebell©™ approach is a low-risk, robust approach that has the potential to de-risk and accelerate clinical drug development and improve the delivery of medications to patients.

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