BMJ Open

A unified multi-level model approach to assessing patient responsiveness including; return to normal, minimally important differences, and minimally clinical important differences for patient reported outcome measures.

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2016-014041
Article Type:	Research
Date Submitted by the Author:	26-Aug-2016
Complete List of Authors:	Sayers, Adrian; University of Bristol, Muscloskeletal Research Unit Wylde, Vikki; University of Bristol, School of Clinical Sciences Lenguerrand, Erik; University of Bristol School of Clinical Science, School of Clinical Sciences, Musculoskeletal Research Unit Gooberman-Hill, Rachael; University of Bristol, School of Clinical Sciences Dawson, Jill; University of Oxford, Department of Public Health Beard, David; University of Oxford, Nuffield Dept of Orthopaedics, Rheumatology and Musculoskeletal Sciences Price, Andrew; University of Oxford, Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences Blom, Ashley; University of Bristol, School of Clinical Sciences
Primary Subject Heading:	Research methods
Secondary Subject Heading:	Rheumatology, Epidemiology, Patient-centred medicine
Keywords:	Patient Responsiveness, Multi-level Modelling, Return To Normal, Minimal Important Difference, Minimal Clinically Important Difference, Patient-reported outcomes

A unified multi-level model approach to assessing patient responsiveness including; return to normal, minimally important differences, and minimally clinical important differences for patient reported outcome measures.

Sayers A[1,2], Wylde V[1], Lenguerrand E[1], Gooberman-Hill R[1], Dawson J[3], Beard D[4], Price A[4], Blom AW[1]

Address for Correspondence

Adrian Sayers, Musculoskeletal Research Unit, School of Clinical Sciences, University of Bristol, Learning and Research Building (Level 1), Southmead Hospital, Westbury on Trym, Bristol, BS10 5NB

E-mail: adrian.sayers@bristol.ac.uk

Tel: 44 (0)117 4147880; Fax + 44(0)117 414 7924

1. Musculoskeletal Research Unit, School of Clinical Sciences, University of Bristol, Southmead Hospital, Westbury On Trym, Bristol, BS10 5NB (AS, VW, EL, RGH, AWB).
2. School of Social and Community Medicine, University of Bristol, 39 Whatley Road, Bristol, BS8 2PS.
3. Nuffield Department of Population Health, University of Oxford, Old Road Campus, Headington, Oxford OX3 7LF, UK (DB, AP).
4. Biomedical Research Unit, Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Science, Nuffield Orthopaedic Centre, Windmill Road, Oxford, OX2 9JA (JD).

Word Count 4010

Keywords: Patient Responsiveness, Multi-level Modelling, Return To Normal , Minimal Important Difference, Minimal Clinically Important Difference, Patient-reported outcomes, Clinical significance Anchor-based methods; Distribution based methods

Abstract (271 Words)

Objective

This article reviews four commonly used approaches to assess patient responsiveness to a treatment or therapy [Return To Normal (RTN), Minimal Important Difference (MID), Minimal Clinically Important Difference (MCID), OMERACT-OARSI (OO)], and demonstrates how each of the methods can be formulated in a multi-level modelling (MLM) framework.

Design

Cohort Study

Setting

A cohort of patients undergoing total hip and knee replacement were recruited from a single UK NHS hospital.

Population

400 Patients from The Arthroplasty Pain Experience (APEX) cohort study undergoing total hip (n=210) and knee (n=190) replacement who completed the Intermittent and Constant Osteoarthritis Pain (ICOAP) questionnaire prior to surgery and then at 3, 6 and 12 months after surgery.

Primary Outcomes

The primary outcome was defined as response to treatment following total hip or knee replacement. We compared baseline scores, change scores, and proportion of individuals defined as “responders” using traditional and MLM approaches to patient responsiveness.

Results

Using existing approaches, baseline and change scores are underestimated, and the variance of baseline and change scores overestimated in comparison to MLM approaches. MLM increases the proportion of individuals defined as responding in RTN, MID, and OO criteria compared to existing approaches. Using MLM with the MCID criteria reduces the number of individuals identified as responders.

Conclusion

MLM improves the estimation of the standard deviation of baseline and change scores by explicitly incorporating measurement error into the model, and avoiding regression to the mean when making individual predictions. Using refined definitions of responsiveness may lead to a reduction in misclassification when attempting to predict who does and does not respond to an intervention, and clarifies the similarities between existing methods.

Article Summary

Strengths and limitations of this study

- Four different approaches to patient responsiveness can be unified into a multi-level modelling.
- A multi-level model framework of patient responsiveness highlights the similarities and differences between existing methods.
- Multi-level models provide a simple framework which incorporates measurement error and non-linear change in trajectories of patient recovery.
- Multi-level models are technically more demanding than existing formulations of patient responsiveness, and convergence is not guaranteed.
- Multi-level models does not improve the arbitrary placement of the thresholds that define responsiveness in comparison to existing methods

INTRODUCTION

Joint replacement is an increasingly common elective procedure worldwide [1-3] and improving patient reported outcomes after joint replacement is a key research priority due to high prevalence of poor outcomes after joint arthroplasty.[4] Poor outcomes include continuing pain, functional limitations,[5] and increased healthcare utilisation.[6] However, there is some debate on how the efficacy of interventions can be judged due to the variety of different outcomes used in orthopaedic research.[7-18] Traditionally, objective primary outcomes such as prosthetic survivorship and mortality rates were used.[19] However, more recently there has been a shift in focus which ensures that patients' perspective is central to assessment of intervention success.[20] Many studies now use patient reported outcome measures (PROMs) as endpoints, and these tools can assess a variety of health outcomes, including pain,[7 21] physical functioning,[7] mental well-being[22] and health-related quality of life.[23]

Although PROMs are widely used,[4] there is still debate in how the results should be interpreted and how to define a clinically meaningful change.[24-35] From a measurement perspective, the ability to estimate if a change has occurred depends on the application of an appropriate statistical model. From a clinical perspective, some authors suggest that the average statistical change is insufficient to "tell you anything about an individual's chances of improving".[36] Therefore, the utility of simple statistical analyses are limited when attempting to help patients weigh up the risks and benefits of undergoing surgery.

In order to supplement simple statistical analysis, many researchers attempt to dichotomise the population into those who have or have not responded to an intervention. There are a number of different methods (definitions) that can be used to dichotomise the population, and these secondary analyses are collectively referred to as responsiveness analyses.[36] Four substantively different methods of estimating the proportion of individuals who respond to an intervention have been previously identified in orthopaedic research:[36] 1) Return to Normal (RTN), 2) Distribution-based

Minimally Important Difference (MID), 3) Anchor-based Minimal Clinically Important Difference (MCID), and 4) the OMERACT-OARSI (OO) responder criteria. The first three approaches are generic and used in many fields of health research, whereas the fourth approach is specific to orthopaedic research, but in principle could be used in many fields of health research.

Each of these approaches is often thought to be methodologically distinct. However, all of the methods can be shown to be special cases of a multi-level model (MLM). In this paper we will describe these four approaches to calculating responsiveness and highlight the substantively different decisions each method makes. We will then describe how each approach can be translated into a MLM framework, emphasising the benefits of the translation, and contrast the approaches using an example from the APEX cohort study.[37]

METHODS

We outline the four existing approaches to patient responsiveness previously used in orthopaedic research [36], and describe their potential limitations, and how they can formulated in a MLM framework.

Review of existing approaches to responsiveness

Return to normal (RTN)[26] suggests that an individual has returned to 'normal' if their score on a post-intervention outcome is greater than two standard deviations (SD) from the mean baseline response.

The use of two standard deviations appears to be justified on theoretical grounds, however it is quite arbitrary. Assuming scores are normally distributed and measured without error, two SD's corresponds to a 95.5% prediction interval for the mean, which is similar to the equally arbitrary and much criticised significance threshold p=0.05 (Type I error=0.05) criterion used throughout medical research[38 39]. However, there is no reason why a 1.6 or a 2.6 SD cut-offs should not be used in preference, which correspond to 90% and 99% prediction intervals.

The method also assumes the observed change is unlikely to be due to chance alone and does not account for any uncertainty. In order to alleviate this problem the use of the Relative Change Index (RCI) was proposed to be used in conjunction with the RTN classification.[24 27] The RCI constructs a test of the individual's score at follow up compared to their baseline, where the standard error of the difference is estimated indirectly using the SD of the baseline score and an assumed reliability coefficient from empirical research or a range of reliability values in the spirit of a sensitivity analysis.

A commonly described distribution-based Minimally Important Difference (MID) method classifies individuals as responders if their observed change is greater than a fixed proportion of the SD of the pre-post-surgery change score.[33] There has been much debate about the exact size, or proportion, of the SD change score to use, however 0.5 SD's has been reported widely and suggested to be a

difference that is minimally perceptible to patients.[30] Any individual with a change score greater than 0.5 SD is defined as responding to the treatment. Similar to the RTN criteria, the decision to use 0.5 is arbitrary and there is no reason why more or less stringent criteria of 0.25, 1 or 2 SD's could not be used.

Anchor-based Minimally Clinically Important Difference (MCID) is similar to the MID approach, in that it defines an individual as a responder based on their individual change score. However, the cut-point is determined in individuals who report themselves as having an outcome which is either good/satisfactory or perceived as improved from baseline using an external anchoring question. The authors proposed using a cut point at the 75th centile of the change score, in those who are satisfied.[35] Therefore any individuals, whether they are satisfied or not, who has a change score greater than the 75th centile are defined as responders.

The OMERACT-OARSI (OO) criteria[32] recognises that a response to an intervention may occur in one or more different measured outcomes, i.e. a multivariate response mechanism. In keeping with much of the orthopaedic literature they assume the proposed score has been rescaled between 0 and 100 [32], and that a responder is defined as any individual with 1. a >=50% relative change or a >=20 point absolute change on one or more responses scales, or 2. a >=20% relative change or >=10 point absolute change in two or more response scales. Relative change is defined as the ratio of the change to the individual baseline score multiplied by 100. Unlike the RTN, MID, or MCID it is very clear that the thresholds for relative and absolute changes are based on a panel of expert opinions and are fixed.

Despite the variety of existing approaches used to identifying responders there are a number of problems common to all methods. Common assumptions include: 1) Each observed outcome is measured without error, test-retest reliability studies indicate that this is not a realistic assumption .[40] 2) Regression to the mean does not occur and therefore the variance of the change score will not

be overestimated. 3) Floor and ceiling effects do not bias estimates of the variance of the change score.[41]

Furthermore in RTN, specific combinations of means and variances may result in a threshold beyond the range of the measurement tool, therefore no individuals would be defined as responding to a therapy. The MCID approach assumes the additional anchoring variable is measured without error and the response trajectory is distinct from those who are unsatisfied.[42] The method also assumes a two parameter logistic function is an appropriate model for the cumulative proportional rank of patients and change in outcome, and that there is no uncertainty in the calculation of the threshold .[43] Finally, the OO approach considers a response in two or more outcomes. However, it does not explicitly describe how the correlation between the two outcomes is accounted for, and fails to recognise that if not modelled appropriately may introduce bias.[44-46]

The four methods identified have a number of other limitations,[25] but they are difficult to compare methods when presented as distinct approaches.

Embedding them in a unified statistical framework makes their underlying assumptions explicit, whilst highlighting their similarities and differences. In addition, it provides a framework to incorporate non-linear change, measurement error, and variability in the timing of measurement occasions.

Multi-level modelling approach to responsiveness

We now present a general multi-level model for patient responsiveness and show how the four approaches described above can be specified as special cases.

Under the assumption of linear change, the measured response at the i^{th} occasion for the j^{th} individual is modelled as a linear function of time.

Equation 1

$$y_{ij} = \beta_0 + u_{0j} + (\beta_1 + u_{1j})t_{ij} + \varepsilon_{ij}$$

$$\begin{bmatrix} u_{0j} \\ u_{1j} \end{bmatrix} \sim N(0, \Omega_u), \qquad \Omega_u = \begin{bmatrix} \sigma^2_{u0} & \\ \sigma_{u01} & \sigma^2_{u1} \end{bmatrix}$$

$$[\varepsilon_{ij}] \sim N(0, \sigma^2_\varepsilon)$$

where t_{ij} is the time at which measurement i was taken on individual j, coded as zero at baseline. β_0 is the baseline population average response, and u_{0j} represents the j^{th} individual difference from the baseline response. The sum of $\beta_0 + u_{0j}$ is the estimated individual baseline response. β_1 represents the population average change per unit increase in time , and u_{1j} represents the j^{th} individual difference from the population average change per unit increase in time. The sum of $\beta_1 + u_{1j}$ is the estimated individual average change per unit increase in time. Measurement error in the linear trajectory is represented by ε_{ij} .

The variance in individual deviations from the population average response at baseline and average rate of change are σ^2_{u0} and σ^2_{u1} respectively. Furthermore, the correlation between baseline measurements and rate of change can be assumed to be independent or correlated by constraining σ_{u01} to be zero or allowing it to be freely estimated. The variances of the shrunken residuals $\hat{u}_{0j}$ and $\hat{u}_{1j}$, also known as empirical bayes estimates, are typically less than the estimated population variances $\hat{\sigma}^2_{u0}$ and $\hat{\sigma}^2_{u1}$ as they shrink towards the population averages of β_0 and β_1 . The extent of the shrinkage depends on the number of measurement occasions and the within individual variability, with greater shrinkage as the number of measurement occasions decrease and as the within individual variance increases. A more detailed discussion of MLM can be found in most advanced statistics textbooks.[44 47 48]

We now describe how the four traditional approaches to measuring patient responsiveness can be unified into a MLM framework. General benefits of the MLM approach include: 1) with more than

three measurement occasions a MLM directly allows for measurement error, ε_{ij} ; 2) the use of shrunken residuals $\widehat{u_{0j}}$ and $\widehat{u_{1j}}$ allow for regression to the mean when predicting an individual's score [49]; 3) MLM can be extended to include multivariate response models which appropriately model the correlation between two or more outcomes; and 4) MLM allows for variability in the timing of measurement occasions.

MLM-Return To Normal. In order to apply the RTN criteria using a MLM approach we first estimate the baseline population SD in individuals considered to be abnormal using the model described in Equation 1. Assuming y_{ij} is normally distributed at baseline with a population mean β_0 and variance σ_{u0}^2 a $100 \cdot \left(1 - \frac{\alpha}{2}\right)$ prediction interval for the baseline measurement can be constructed i.e. $\left[\beta_0 - \sigma_{u0}\mathrm{z}_{\left(1-\frac{\alpha}{2}\right)}, \beta_0 + \sigma_{u0}\mathrm{z}_{\left(1-\frac{\alpha}{2}\right)}\right]$ where α is the type I error rate and z is the critical value from a standard normal distribution. Importantly y_{ij} is not assumed to be measured without error and therefore estimates of σ_{u0}^2 are less likely to be biased than using simple methods. However, it is important to note that the choice of α is entirely that of the researcher, and whilst α =0.05 (leading to $z = 1.96 \approx 2$) is common, more or less stringent criteria could be applied.

The second step is to estimate the score of the individual at time *j* following surgery and determine if it is within the baseline prediction interval. This prediction is simply calculated by substituting estimates of β_0 , β_1 , u_{0j} and u_{1j} into Equation 1, to give the empirical best linear unbiased prediction (eBLUP) for the j^{th} individual at the i^{th} occasion.[50]

Finally, in order to determine whether or not the response of the individual following surgery is greater than one would attribute to chance alone, i.e. the null hypothesis that the j^{th} individuals slope is not equal to zero, a test statistic similar to RCI should be conducted,

$\left(\hat{\beta}_1 + \hat{u}_{1j}\right)/SE\left(\hat{\beta}_1 + \hat{u}_{1j}\right)$, where $SE\left(\hat{\beta}_1 + \hat{u}_{1j}\right) = \sqrt{VAR\left(\hat{\beta}_1\right) + VAR\left(\hat{u}_{1j}\right)}$.

MLM-Minimally Important Difference. The threshold of minimally important difference can also be estimated using a MLM. Similar to RTN, a linear model of change is applied, as in Equation 1. Then the population SD of the change score per unit increase in *t* is estimated by σ_{u1}. For example, if t is coded in months and responsiveness at 3 months post-surgery was of interest, the estimated SD of the change score at 3 months would be $3\sigma_{u1}$, and the threshold of responsiveness would be $3\sigma_{u1}/2$. By comparing the estimated change for the j^{th} individual $(\hat{\beta}_1 + \hat{u}_{1j})t$ to the chosen threshold at time *t*, i.e. $t\sigma_{u1}/2$, the individual can be classed as a responder or not. The MID approach does not specifically state whether a test of whether an individual's change scores is less than the MID threshold should be conducted, but a test statistic is simply constructed as

$$\left((\hat{\beta}_1 + \hat{u}_{1j})t - \left(\frac{t\hat{\sigma}_{u1}}{2}\right)\right) \Big/ (SE(\hat{\beta}_1 + \hat{u}_{1j})t).$$

MLM-Minimally Clinically Important Difference. The MLM MCID requires a simple extension of the univariate model presented previously (Equation 1). The outcome of interest is stratified using an external criterion. The stratification is achieved by creating dummy variables for those who are un/satisfied with some aspect of their treatment i.e. x_{1i} takes the values 0 and 1 representing unsatisfied and satisfied individuals respectively, and $x_{2i} = 1 - x_{1i}$. These dummy variables are then included as additional explanatory variables, with no overall model intercept, and interacted with *t.*

Equation 2

$$y_{ij} = (\beta_0 + u_{0j})x_{1i} + (\beta_1 + u_{1j})t_{ij}x_{1i} + \varepsilon_{1ij}x_{1i}$$

$$+ (\beta_2 + u_{2j})x_{2i} + (\beta_3 + u_{3j})t_{ij}x_{2i} + \varepsilon_{2ij}x_{2i}$$

$$\begin{bmatrix} u_{0j} \\ u_{1j} \\ u_{2j} \\ u_{3j} \end{bmatrix} \sim N(0, \Omega_u): \qquad \Omega_u = \begin{bmatrix} \sigma_{u0}^2 & & & \\ \sigma_{u01} & \sigma_{u1}^2 & & \\ 0 & 0 & \sigma_{u2}^2 & \\ 0 & 0 & \sigma_{u23} & \sigma_{u3}^2 \end{bmatrix}$$

$$\begin{bmatrix}\varepsilon_{1ij}\\ \varepsilon_{2ij}\end{bmatrix} \sim N\left(0, \Omega_{\varepsilon}\right): \qquad \Omega_{\varepsilon} = \begin{bmatrix}\sigma^2_{\varepsilon 1} & \\ 0 & \sigma^2_{\varepsilon 2}\end{bmatrix}$$

Therefore β_0 and β_2 are the mean population outcome score at baseline for those who are satisfied and unsatisfied respectively, and β_1 and β_3 are the corresponding mean population changes per unit of time. Variances and covariances are similarly interpreted for those who are satisfied and unsatisfied respectively. However, that satisfaction on the external anchoring question is assumed to be known without error, and individual effects and errors for x_{1i} are uncorrelated with those for x_{2i} because the satisfied and unsatisfied categories are mutually exclusive.

Following prediction of each individual's trajectory, the second stage in the MCID method requires a threshold for determining responsiveness. Using a similar suggestion to Tubach et al.,[35] the 75th centile of those who are satisfied could be used to classify all individuals as responding or not. Similar to the MID there is no suggestion of whether a test against the null value of the 75th centile should be constructed, but this is easily done within the MLM framework.

MLM-OMERACT-OARSI criteria. The OO criteria can be similarly extended into a multi-variate MLM framework by the inclusion of dummy variables and reshaping into a "double" long format with both responses stored in a single vector. Figure 1 illustrates the data structure for a bivariate model.

Figure 1

Single long

j	*t*	y_1	y_2
1	1	40	70

Double Long

j	*t*	*y*	w_1	w_2
1	1	40	1	0
1	2	50	1	0
1	3	60	1	0

1	2	50	80	<---------->	1	4	70	1	0
1	3	60	90		1	1	70	0	1
1	4	70	100		1	2	80	0	1
					1	3	90	0	1
					1	4	100	0	1

Dummy variables, also known as response indicators, are used to denote the response options: w_{1i} is coded 1 for the first measurement outcome (pain) and 0 for the second outcome (function), and $w_{2i} = 1 - w_{1i}$. The response indicators and their interactions with t are included as explanatory variables to obtain the following bivariate response model.

Equation 3

$$y_{ij} = (\beta_0 + u_{0j})w_{1i} + (\beta_1 + u_{1j})t_{ij}w_{1i} + \varepsilon_{1ij}w_{1i}$$

$$+ (\beta_2 + u_{2j})w_{2i} + (\beta_3 + u_{3j})t_{ij}w_{2i} + \varepsilon_{2ij}w_{2i}$$

$$\begin{bmatrix} u_{0j} \\ u_{1j} \\ u_{2j} \\ u_{3j} \end{bmatrix} \sim N(0, \Omega_u): \qquad \Omega_u = \begin{bmatrix} \sigma_{u0}^2 & & & \\ \sigma_{u01} & \sigma_{u1}^2 & & \\ \sigma_{u02} & \sigma_{u12} & \sigma_{u2}^2 & \\ \sigma_{u03} & \sigma_{u13} & \sigma_{u23} & \sigma_{u3}^2 \end{bmatrix}$$

$$\begin{bmatrix} \varepsilon_{1ij} \\ \varepsilon_{2ij} \end{bmatrix} \sim N(0, \Omega_\varepsilon): \qquad \Omega_\varepsilon = \begin{bmatrix} \sigma_{\varepsilon1}^2 & \\ \sigma_{\varepsilon12} & \sigma_{\varepsilon2}^2 \end{bmatrix}$$

With a similar functional form to the univariate MLM, there are separate population and individual intercepts for the first and second outcome (β_0 , β_2 and u_{0j}, u_{2j} respectively), and separate population and individual slopes are estimated for the second outcome $(\beta_1$, β_3 and $u_{1j}, u_{3j})$. Using a MLM approach the outcomes are modelled jointly, which allows for non-zero covariances

between the intercepts and slopes of the two responses ($\sigma_{u02}, \sigma_{u12}, \sigma_{u03}, \sigma_{u13}$). The measurement errors for the two responses are not assumed to be independent, with their covariance directly estimated ($\sigma_{\varepsilon 12}$).

Finally, the threshold of response must be decided and individual trajectories estimated and classified. Similar to the other methods it is relatively simple to construct a test statistic for testing whether individual slopes are significantly different from the chosen threshold.

Limitations of the MLM approach. The MLM approach described by Equation 1, Equation 2 and 3 assumes that change in the outcome is linearly associated with time. The linearity assumption is imposed for simplicity. Non-linear changes are easily incorporated by including higher order polynomials or using linear or non-linear splines.[51]

The standard MLM approach also fails to directly address the issue of floor and ceiling effects. Mixed response multi-level tobit models allow for such effects and provide some adjustment.[41 52] Furthermore, whilst the MLM described in Equation 2 allow for heterogeneity in known groups, they fail to allow for heterogeneity in trajectories when the groups are unknown. The use of group based trajectory models or growth mixture models in these circumstances may reveal latent (unobserved) classes of individuals with distinct patterns of recovery.[53]

Example: The APEX cohort Study

Using a mixed cohort of patients undergoing THR and TKR, [37] we investigated the performance of the existing and MLM approaches using four definitions of responsiveness. A simulated dataset and code to fit each of these models is included in supplementary material.

Patients in the APEX cohort completed the Intermittent and Constant Osteoarthritis Pain (ICOAP) questionnaire before and after surgery at approximately 0, 3, 6 and 12 months. The date at which the post-surgical questionnaire was completed is recorded in days post-surgery. As the name suggests, the ICOAP questionnaire attempts to measure intermittent and constant pain. [21] The developers of the tool suggest three ways of summarising the scale to generate an intermittent, constant and total pain scores (the sum of the intermittent and constant pain subscales). The tool is scored between 0 and 100 and a full description of the ICOAP scale is provided in the original validation paper.[21]

Using the three methods of aggregation, we present estimates of pain at baseline and for change at approximately 3 months post-surgery using summary statistics and multi-level model estimates.

In order to facilitate comparisons between existing and MLM approaches we assume that all individuals are measured at exactly 0, 3, 6, and 12 months. Whilst the existing approaches only utilises the 0 and 3 month measurements the MLM approach uses a growth model using two linear splines with a knot point at 3 months. The inclusion of the second spline and the additional two measurement occasions allows adjustment for measurement error in the MLM approach. Table 1 and 2 presents results for patients undergoing THR and TKR respectively.

RESULTS

In all subdivisions of the ICOAP questionnaire, for THR/TKR patients, the estimates of the baseline mean and change scores are approximately equal to those from the MLM approaches. In addition, estimates of the SD of baseline and change score are overestimated using existing approaches in THR/TKR patients. The SD of baseline measurements is approximately 3.3 and 3.75 points greater than conventional methods in THR/TKR patients respectively, while the corresponding SD of change are approximately 6.3 and 7 points greater than existing methods.

Return To Normal

Using similar baseline score estimates to the conventional RTN approach and different SD's results in a reduction in the threshold of response by approximately 5 points in THR/TKR patients. The change in threshold is due to smaller estimates of baseline and change SD's. When considering the total ICOAP score, the MLM approach classifies approximately 10% more individuals as responders than existing approaches. It is also interesting to note that the threshold of response using the existing approach when considering total ICOAP score in THR patients is beyond the range of the score.

Minimally Important Difference

Using similar change score estimates and different SD's results in an approximately 2 point reduction in the MID threshold in THR/TKR patients. The reduced threshold results in more individuals being classified as responders using the MLM approach.

Minimally Clinically Important Difference

Using the MLM approach in satisfied and unsatisfied individuals results in a small increase in the threshold of response in comparison to existing approaches. The increase in threshold is due to shrunken residuals and therefore reduced variability of predicted change scores. The increase in

threshold results in a reduced number of individuals (3% of THR patients and 6% of TKR patients) being identified as responders.

OMERACT-OARSI

The OO approach uses fixed definitions of responsiveness. Individual estimates of change from the bivariate MLM for constant and intermittent pain are very similar to those from the univariate MLM. However the standard deviation of the change score is reduced by approximately 0.5 and 1 points in constant and intermittent pain comparing the univariate and bivariate MLM respectively, whereas the SD of baseline score approximately the same. Despite the larger absolute threshold of 20 and 10 points for changes in 1 or 2 items respectively, i.e. larger than MID, there is an increase in the proportion of individuals identified as responding. The increase is partly due to the use of the relative change threshold, and the reduced variability in change in comparison to the univariate MLM using MID definition of responsiveness.

DISCUSSION

The primary purpose of a responsiveness analysis is to convey the variability of an individual's chances of perceiving an improvement following a treatment. Existing approaches appear to be distinct from one another, and the relationships between each approach were unclear.

We have clearly shown how four commonly used approaches can be incorporated into the unified statistical framework of MLM. The application of patient responsiveness models in a cohort of orthopaedic patients illustrates how SD's of baseline and change scores in existing approaches are overestimated in comparison to the MLM approach. Thresholds for defining responders from MLM are lower when based on SD (RTN & MID), and higher when based on the distribution of predicted change scores (MCID).

Strengths & Limitations

One of the key benefits of adopting a MLM approach when defining clinically meaningful change is the improved estimation of individual change by the greater flexibility in the MLM framework. Specifically, MLM do not assume the response is measured without error, they adjust for regression to the mean, the trajectory of recovery is not constrained to be linear, and data from multiple measurements and variability in the timing of those measurement occasions can also be incorporated into the model. Furthermore, assuming the underlying MLM adequately represents the true causal mechanism, parameter estimates, SD's and standard errors will be unbiased in comparison to existing approaches.

Furthermore, the unification of existing approaches into a MLM framework clearly shows the relationship between the four different approaches. For example, RTN and MID share the same underlying model. MCID is also the same at RTN/MID if you assume the baseline and change scores are the same across strata of un/satisfied patients. Similarly, the model underlying OO approach is

the same as the RTN/MID approach if you assume independence in the measured outcomes of the two trajectories, and error term.

Despite the numerous benefits of adopting a MLM approach, it is not to say it is without some limitations. MLM are technically more demanding than existing formulations of patient responsiveness, and whilst there are no theoretical limits on how large or small samples have to be, model convergence is not guaranteed. Furthermore, it is important to perform model diagnostic to check the data fit with the model. MLM does not improve the arbitrary placement of the thresholds that define responsiveness in comparison to existing methods, and despite the improved trajectory modelling it is currently unclear if the refined definitions correlate more strongly with patient expectations or functional data. Further research externally validating the classification using patient groups, expert opinion[54] or functional data may demonstrate improved classification of those responding to treatment in comparison to existing methods.

It is clear the MLMs provide considerable advantages over existing approaches to identifying patients who respond to a treatment. Consequently, the proportion of individuals thought not to be responding to treatment may be smaller than previously thought. Using the redefined definition may reduce the number of individuals misclassified as non-responders, and improve the prediction of those individuals who are likely to respond to treatment.

Abbreviations

APEX – Arthroplasty Pain Experience

ICOAP - Intermittent and Constant Osteoarthritis Pain

MCID – Minimally Clinical Important Difference

MID – Minimal Important Difference

MLM – Multi Level Model

OO – OMERACT OARSI Criteria

RCI – Relative Change Index

RTN – Return To Normal

SD – Standard Deviation

SE – Standard Error

THR – Total Hip Replacement

TKR – Total Knee Replacement

Acknowledgements

We would like to thank Professor Fiona Steele for her extensive comments and help preparing this manuscript.

Author Contributions

Study Conception (AS). APEX study design (VW, RGH, AWB). APEX acquisition of data (VW, RGH, AWB, EL). ACHE study design (JD, DB, AP). Wrote first draft & revised manuscript (AS). Drafting and review of manuscript (AS, VW, RGH, AWB, EL, JD, DB, AP). Final approval of Manuscript (AS, VW, RGH, AWB, EL, JD, DB, AP)

Funding Statement

This work was supported by AS is funded by an MRC Fellowship MR/L01226X/1 and HTA Project:11/63/01 – 'ACHE'. This article presents independent research funded by the National Institute for Health Research (NIHR) under its Programme Grants for Applied Research programme (RP-PG-0407-10070). The views expressed in this article are those of the authors and not necessarily those of the NHS, the NIHR or the Department of Health. The research team acknowledge the support of the NIHR, through the Comprehensive Clinical Research Network.

Competing Interest

The Authors have no competing interests to declare.

Data Sharing

No data is available to be shared.

REFERENCES

1. Felson DT, Naimark A, Anderson J, et al. The prevalence of knee osteoarthritis in the elderly. The Framingham Osteoarthritis Study. Arthritis and rheumatism 1987;**30**(8):914-8.
2. Lawrence RC, Felson DT, Helmick CG, et al. Estimates of the prevalence of arthritis and other rheumatic conditions in the United States. Part II. Arthritis and rheumatism 2008;**58**(1):26-35.
3. National Joint Registry. *10th Annual Report 2013*. Hemel Hempstead, 2013.
4. Beswick AD, Wylde V, Gooberman-Hill R, et al. What proportion of patients report long-term pain after total hip or knee replacement for osteoarthritis? A systematic review of prospective studies in unselected patients. Bmj Open 2012;**2**(1).
5. Jeffery AE, Wylde V, Blom AW, et al. "It's there and I'm stuck with it": patients' experiences of chronic pain following total knee replacement surgery. Arthritis care & research 2011;**63**(2):286-92.
6. Kassam A, Dieppe P, Toms AD. An analysis of time and money spent on investigating painful Total Knee Replacements. British Journal of Medical Practitioners 2012;**5**(3).
7. Bellamy N, Buchanan WW, Goldsmith CH, et al. Validation study of WOMAC: a health status instrument for measuring clinically important patient relevant outcomes to antirheumatic drug therapy in patients with osteoarthritis of the hip or knee. The Journal of rheumatology 1988;**15**(12):1833-40.
8. Klassbo M, Larsson E, Mannevik E. Hip disability and osteoarthritis outcome score. An extension of the Western Ontario and McMaster Universities Osteoarthritis Index. Scand J Rheumatol 2003;**32**(1):46-51.
9. Roos EM, Roos HP, Lohmander LS, et al. Knee Injury and Osteoarthritis Outcome Score (KOOS)--development of a self-administered outcome measure. J Orthop Sports Phys Ther 1998;**28**(2):88-96.
10. Dawson J, Fitzpatrick R, Carr A, et al. Questionnaire on the perceptions of patients about total hip replacement. J Bone Joint Surg Br 1996;**78B**(2):185-90.
11. Dawson J, Fitzpatrick R, Murray D, et al. Questionnaire on the perceptions of patients about total knee replacement. J Bone Joint Surg Br 1998;**80B**(1):63-69.
12. Focht BC, Rejeski WJ, Ambrosius WT, et al. Exercise, self-efficacy, and mobility performance in overweight and obese older adults with knee osteoarthritis. Arthritis and rheumatism 2005;**53**(5):659-65.
13. Smith AJ, Dieppe P, Howard PW, et al. Failure rates of metal-on-metal hip resurfacings: analysis of data from the National Joint Registry for England and Wales. Lancet 2012;**380**(9855):1759-66.
14. Smith AJ, Dieppe P, Porter M, et al. Risk of cancer in first seven years after metal-on-metal hip replacement compared with other bearings and general population: linkage study between the National Joint Registry of England and Wales and hospital episode statistics. Bmj 2012;**344**:e2383.
15. Hunt LP, Ben-Shlomo Y, Clark EM, et al. 45-day mortality after 467 779 knee replacements for osteoarthritis from the National Joint Registry for England and Wales: an observational study. Lancet 2014.
16. Hunt LP, Ben-Shlomo Y, Clark EM, et al. 90-day mortality after 409,096 total hip replacements for osteoarthritis, from the National Joint Registry for England and Wales: a retrospective analysis. Lancet 2013;**382**(9898):1097-104.

17. Riddle DL, Stratford PW, Bowman DH. Findings of extensive variation in the types of outcome measures used in hip and knee replacement clinical trials: A systematic review. Arthrit Rheum-Arthr 2008;**59**(6):876-83.
18. Wylde V, Bruce J, Beswick A, et al. Assessment of chronic postsurgical pain after knee replacement: a systematic review. Arthritis care & research 2013;**65**(11):1795-803.
19. Wylde V, Blom AW. The failure of survivorship. The Journal of bone and joint surgery British volume 2011;**93**(5):569-70.
20. Darzi. High quality care for all: NHS Next Stage Review final report, 2008.
21. Hawker GA, Davis AM, French MR, et al. Development and preliminary psychometric testing of a new OA pain measure--an OARSI/OMERACT initiative. Osteoarthritis and cartilage / OARS, Osteoarthritis Research Society 2008;**16**(4):409-14.
22. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. Acta Psychiatr Scand 1983;**67**(6):361-70.
23. Williams A, Kind P. The present state of play about QALYs. In: Hopkins A, ed. Measure of the quality of life: the uses to which they may be put: RCP publications 1992.
24. Christensen L, Mendoza JL. A Method of Assessing Change in a Single Subject - an Alteration of the Rc Index. Behav Ther 1986;**17**(3):305-08.
25. Guyatt GH, Osoba D, Wu AW, et al. Methods to explain the clinical significance of health status measures. Mayo Clinic proceedings 2002;**77**(4):371-83.
26. Jacobson NS, Roberts LJ, Berns SB, et al. Methods for defining and determining the clinical significance of treatment effects: description, application, and alternatives. J Consult Clin Psychol 1999;**67**(3):300-7.
27. Jacobson NS, Truax P. Clinical significance: a statistical approach to defining meaningful change in psychotherapy research. Journal of consulting and clinical psychology 1991;**59**(1):12-9.
28. Kvien TK, Heiberg T, Hagen KB. Minimal clinically important improvement/difference (MCII/MCID) and patient acceptable symptom state (PASS): what do these concepts mean? Annals of the rheumatic diseases 2007;**66 Suppl 3**:iii40-1.
29. Maksymowych WP, Richardson R, Mallon C, et al. Evaluation and validation of the patient acceptable symptom state (PASS) in patients with ankylosing spondylitis. Arthritis and rheumatism 2007;**57**(1):133-9.
30. Norman GR, Sloan JA, Wyrwich KW. Interpretation of changes in health-related quality of life: the remarkable universality of half a standard deviation. Med Care 2003;**41**(5):582-92.
31. Norman GR, Sridhar FG, Guyatt GH, et al. Relation of distribution- and anchor-based approaches in interpretation of changes in health-related quality of life. Medical care 2001;**39**(10):1039-47.
32. Pham T, van der Heijde D, Altman RD, et al. OMERACT-OARSI initiative: Osteoarthritis Research Society International set of responder criteria for osteoarthritis clinical trials revisited. Osteoarthritis and cartilage / OARS, Osteoarthritis Research Society 2004;**12**(5):389-99.
33. Revicki D, Hays RD, Cella D, et al. Recommended methods for determining responsiveness and minimally important differences for patient-reported outcomes. Journal of clinical epidemiology 2008;**61**(2):102-9.
34. Tubach F, Ravaud P, Baron G, et al. Evaluation of clinically relevant changes in patient reported outcomes in knee and hip osteoarthritis: the minimal clinically important improvement. Annals of the rheumatic diseases 2005;**64**(1):29-33.
35. Tubach F, Ravaud P, Baron G, et al. Evaluation of clinically relevant states in patient reported outcomes in knee and hip osteoarthritis: the patient acceptable symptom state. Annals of the rheumatic diseases 2005;**64**(1):34-37.
36. Judge A, Cooper C, Williams S, et al. Patient-reported outcomes one year after primary hip replacement in a European Collaborative Cohort. Arthritis care & research 2010;**62**(4):480-8.

37. Wylde V, Gooberman-Hill R, Horwood J, et al. The effect of local anaesthetic wound infiltration on chronic pain after lower limb joint replacement: A protocol for a double-blind randomised controlled trial. BMC Musculoskelet Disord 2011;**12**:53.
38. Altman DG, Gore SM, Gardner MJ, et al. Statistical guidelines for contributors to medical journals. British medical journal 1983;**286**(6376):1489-93.
39. Sterne JA, Davey Smith G. Sifting the evidence-what's wrong with significance tests? BMJ 2001;**322**(7280):226-31.
40. McConnell S, Kolopack P, Davis AM. The Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC): A review of its utility and measurement properties. Arthrit Rheum-Arthr 2001;**45**(5):453-61.
41. Twisk J, Rijmen F. Longitudinal tobit regression: A new approach to analyze outcome variables with floor or ceiling effects. Journal of clinical epidemiology 2009;**62**(9):953-58.
42. Ram N, Grimm KJ. Growth mixture modeling: A method for identifying differences in longitudinal change among unobserved groups. Int J Behav Dev 2009;**33**(6):565-76.
43. Jones G, Lyons P. Approximate graphical methods for inverse regression. Journal of Data Science 20009;**7**:61-72.
44. Snijders TAB, Bosker RJ. *Multilevel Analysis: An Introduction to Basic and Advanced Multilevel Modeling, second edition*. London: Sage Publishers, 2012.
45. Fieuws S, Verbeke G. Pairwise fitting of mixed models for the joint modeling of multivariate longitudinal profiles. Biometrics 2006;**62**(2):424-31.
46. Fieuws S, Verbeke G. Joint modelling of multivariate longitudinal profiles: pitfalls of the random-effects approach. Statistics in medicine 2004;**23**(20):3093-104.
47. Verbeke G, Molenberghs G. *Linear mixed models for longitudinal data*. USA: Springer, 2000.
48. Rasbash J, Steele F, Browne WJ, et al. *A user's guide to MLwIN*. UK, 2009.
49. Copas JB. Regression, Prediction and Shrinkage. J R Stat Soc B 1983;**45**(3):311-54.
50. Fitzmaurice GM, Laird NM, Ware JH. *Applied Longitudinal Analysis*. USA: Wiley, 2004.
51. Pan HQ, Goldstein H. Multi-level repeated measures growth modelling using extended spline functions. Statistics in medicine 1998;**17**(23):2755-70.
52. Rabe-Hesketh S, Skrondal A. Multilevel and latent variable modeling with composite links and exploded likelihoods. Psychometrika 2007;**72**(2):123-40.
53. Nagin DS, Odgers CL. Group-Based Trajectory Modeling in Clinical Research. Annu Rev Clin Psycho 2010;**6**:109-38.
54. Bellamy N, Carette S, Ford PM, et al. Osteoarthritis antirheumatic drug trials. III. Setting the delta for clinical trials--results of a consensus development (Delphi) exercise. The Journal of rheumatology 1992;**19**(3):451-7.

Table 1: Mean and standard deviation of baseline and change scores estimated using current and multi-level model approaches to responsiveness in patient undergoing total hip replacement in the APEX cohort study. Betas represent the population average characteristic and sigma the estimated standard deviation. Baseline is assumed to be the day of surgery, and change is from 0 to 3.6 months.

			Current Approaches to Responsiveness						Multi-Level Model Approaches to Responsiveness					
			Baseline		Change		Absolute Threshold	P(Resp.)	Baseline		Change		Absolute Threshold	P(Resp.)
		N	β_0	σ_{u0}	β_1	σ_{u1}			β_0	σ_{u0}	β_1	σ_{u1}		
Return to Normal	Total Pain	210	43.71	(22.1)	45.76	(24.0)	87.9	70.5	43.71	(20.1)	46.14	(19.7)	83.8	78.1
MID		210					12.0	90.5					9.9	97.6
MCID (Satisfied)		185	44.37	(22.0)	48.43	(22.6)	32.6	71.9	44.37	(20.3)	48.54	(19.2)	35.8	67.1
MCID (UnSatisfied)		25	38.77	(22.4)	26.05	(25.4)			38.77	(17.0)	28.43	(16.3)		67.1
Return to Normal	Constant Pain	210	49.19	(27.2)	44.23	(27.3)	103.5	0.0	49.19	(25.6)	44.35	(24.0)	100.3	0.0
MID		210					13.6	84.3					12.0	88.6
MCID (Satisfied)		185	50.08	(27.4)	46.37	(26.7)	30.0	72.4	50.08	(26.3)	46.21	(24.5)	31.0	73.3
MCID (UnSatisfied)		25	42.60	(24.8)	28.40	(26.9)			42.60	(18.3)	30.60	(12.6)		
OO		210	49.19	(27.2)	44.23	(27.3)	20(10)	92.0	49.19	(25.3)	44.35	(23.4)	20(10)	99.5
Return to Normal	Intermittent Pain	210	39.13	(21.7)	47.06	(26.5)	82.5	70.0	39.12	(18.7)	47.66	(20.5)	76.5	80.5
MID		210					13.2	88.1					10.3	97.1
MCID (Satisfied)		185	39.60	(21.7)	50.17	(24.9)	37.5	71.4	39.60	(19.2)	50.50	(19.1)	40.5	67.1
MCID (UnSatisfied)		25	35.58	(21.4)	24.08	(26.6)			35.58	(13.9)	26.69	(17.1)		
OO		210	39.13	(21.7)	47.06	(26.5)	20(10)	92.0	39.12	(18.5)	47.66	(19.1)	20(10)	99.5

Table 2: Mean and standard deviation of baseline and change scores estimated using current and multi-level model approaches to responsiveness in patient undergoing total knee replacement in the APEX cohort study. Betas represent the population average characteristic and sigma the estimated standard deviation. Baseline is assumed to be the day of surgery, and change is from 0 to 3.6 months.

			Current Approaches to Responsiveness						Multi-Level Model Approaches to Responsiveness					
			Baseline		Change		Absolute Threshold	P(Resp.)	Baseline		Change		Absolute Threshold	P(Resp.)
		N	β_0	σ_{u0}	β_1	σ_{u1}			β_0	σ_{u0}	β_1	σ_{u1}		
Return to Normal	Total Pain	190	42.86	(19.7)	31.27	(23.2)	82.3	43.2	42.89	(16.7)	32.09	(17.7)	76.3	51.6
MID		190					11.6	76.3					8.9	93.2
MCID (Satisfied)		138	44.09	(19.7)	38.51	(20.6)	22.7	62.6	44.13	(16.7)	38.76	(14.7)	29.9	55.3
MCID (UnSatisfied)		52	39.62	(19.7)	12.04	(18.0)			39.62	(16.3)	14.28	(11.5)		
Return to Normal	Constant Pain	190	47.76	(23.6)	31.61	(25.5)	94.9	44.7	47.79	(20.5)	32.46	(19.5)	88.7	36.8
MID		190					12.8	74.7					9.7	90.0
MCID (Satisfied)		138	48.80	(23.4)	38.59	(23.3)	23.7	64.2	48.88	(20.5)	38.88	(17.7)	30.3	55.3
MCID (UnSatisfied)		52	45.00	(24.1)	13.08	(21.9)			45.00	(20.1)	15.26	(13.3)		
OO		190	47.76	(23.6)	31.61	(25.5)	20(10)	78.9	47.78	(20.2)	32.50	(18.9)	20(10)	98.4
Return to Normal	Intermittent Pain	190	38.78	(18.2)	30.97	(23.9)	75.3	40.5	38.80	(13.8)	31.77	(16.7)	66.4	62.1
MID		190					12.0	78.4					8.3	94.2
MCID (Satisfied)		138	40.15	(18.3)	38.45	(21.2)	24.8	61.6	40.20	(14.1)	38.63	(12.8)	31.2	54.7
MCID (UnSatisfied)		52	35.14	(17.8)	11.12	(19.0)			35.14	(12.8)	13.40	(10.8)		
OO		190	38.78	(18.2)	30.97	(23.9)	20(10)	78.9	38.81	(13.6)	31.74	(15.7)	20(10)	98.4

```
*******************************************************************************
***
*  A unified multi-level model approach to assessing patient responsiveness
*  including; return to normal, minimally important differences, and minimally
*  clinical important differences for patient reported outcome measures.
*******************************************************************************
***
*
*  Sayers A*, Wylde V, Lenguerrand E, Gooberman-Hill R, Dawson J, Beard D,
*  Price A, Blom AW
*
*  1.     Musculoskeletal Research Unit, School of Clinical Sciences,
*       University of Bristol, Southmead Hospital, Westbury On Trym,
*                 Bristol, BS10 5NB.
*  2.     Nuffield Department of Population Health, University of Oxford,
*                 Old Road Campus, Headington, Oxford OX3 7LF, UK
*  3.     Biomedical Research Unit, Nuffield Department of Orthopaedics,
*                 Rheumatology and Musculoskeletal Science, Nuffield
Orthopaedic Centre,
*                 Windmill Road, Oxford, OX2 9JA
*
*        Address for Correspondence
*   Adrian Sayers, Musculoskeletal Research Unit, School of Clinical Sciences,
*   University of Bristol, Learning and Research Building (Level 1),
*   Southmead Hospital, Westbury on Trym, Bristol, BS10 5NB
*
*
*   E-mail: adrian.sayers@bristol.ac.uk
*   Tel: 44 (0)117 4147880; Fax + 44(0)117 414 7924
*******************************************************************************
***
* Abstract
* Stata code to illustrate calculation of patient reponsiveness using existing
* and multi-level model methods.
* Do file should be run comlpletely inorder to simulate data from a linear
model
* and perform calculations.
* File requires MLWin and copy of runmlwin downloaded for Stata.

*******************************************************************************
***
* 1. Simulate a dataset
*******************************************************************************
***
{
* Design matrix in OO Format
set seed 111
clear
set obs 100

gen id= _n

* Set Parameters values
         * Set Fixed Effect Parameters
         local b0 = 49.19
                  local b1 = 44.35 / 3
                           local b2 = 39.12
                                    local b3 = 47.66 / 3
* Set Random Effect Standard Deviations & Correlation Matrix
local u0 = 25.3
```

```
          local u1 = 23.4 / 3
                    local u2 = 18.5
                              local u3 = 19.1 / 3
                                        matrix u = (`u0',`u1',`u2',`u3')'
                                                  matrix u_corr = (1   ,0.3 ,0.1
,0.1 \  ///

0.3 ,1   ,0.1 ,0.1 \  ///

0.1 ,0.1 ,1   ,0.3 \  ///

0.1 ,0.1 ,0.3 ,1   )
* Draw Random Parameters
          drawnorm u0 u1 u2 u3 , sds(u) corr(u_corr)


* Create 4 measurement occassions

expand 4
by id , sort : gen t = _n-1

* Prepare for a reshape into double long
gen _1= 1
          gen _2= 1
                    reshape long _ , i(id t) j(resp)
                              drop _

* Set error Standard Deviations & Correlation Matrix
local e1= 5
          local e2= 5
                    matrix e = (`e1', `e2')'
                              matrix e_corr = (1   ,0.1 \  ///
                                                            0.1 ,1
)  //

                                        drawnorm e1 e2 , sds(e) corr(e_corr)


* Create response indicators for OO
gen w1 = 1 if resp==1
          replace w1 = 0 if resp==2
                    gen w2 = 0 if resp==1
                              replace w2 = 1 if resp==2

* Generate a satisfaction indicator, uncorrelated with effects just for
illustration
gen x = cond(uniform()>=0.3,1,0) if resp==1 & t==1
          by id : egen _x = min(x)
                    *Create dummy variables
                              gen x1 = 1 if _x==1
                                        replace x1 = 0 if _x==0
                                                  gen x2 = 0 if _x==1
                                                            replace x2 = 1 if
_x==0
                                                                      drop x _x


* Predict response
gen y = (`b0' + u0)* w1 + (`b1' + u1)* w1 * t + e1* w1 + ///
                    (`b2' + u2)* w2 + (`b3' + u3)* w2 * t + e2* w2 //
```

```
tempfile simdata
          save `simdata' , replace

}
*******************************************************************************
***
* 2.1 Existing Methods (n.b. only for first response)
*******************************************************************************
***
use  `simdata' , clear
          * Working with the first and last measurment occassion
                    keep if  t ==0 | t==3
                              sort id resp t
                                        by id resp : gen d_y = y[_n] - y[_n-1]
*********************
* 2.1.1 Existing RTN
*********************
{
          sum y if t==0 & resp==1
                    local rtn = r(mean) + 2*r(sd)
                              by id resp: gen ex_rtn =cond(y>=`rtn',1 ,0) if
_n==2 & resp==1
                                        by id resp: gen ex_rci = cond((d_y /
sqrt(2*(`r(sd)' * sqrt(1-0.9))^2))>=1.96,1,0) if _n==2 & resp==1
                                                  by id resp: gen ex_rtn_rci =
cond(ex_rtn==1 & ex_rci==1 ,1,0) if _n==2 & resp==1

                                                  tab ex_rtn if resp==1
// Number of individuals returning to normal
                                                  tab ex_rci if resp==1
// Number of individuals significant change
                                                  tab ex_rtn_rci if resp==1
// Number of individuals significant change & returning to normal
                                                  }
*********************
* 2.1.2 Existing MID
*********************
{
su d_y if resp==1
          local mid = r(sd)*0.5
                    by id resp : gen ex_mid =cond(d_y>=`mid',1,0)  if _n==2 &
resp==1

                              tab ex_mid if resp==1                    // Number
of individuals with minimally important difference
}
*********************
* 2.1.3 Existing MCID
* n.b using the 25th centile is pain is reverse coded.
*********************
{
centile d_y if resp==1 & x1==1 , c(25)
          local mcid = r(c_1)
                    by id resp: gen ex_mcid = cond(d_y>=`mcid',1,0) if _n==2 &
resp==1

                              tab ex_mcid if resp==1       // Number of
individuals meeting the MCID criteria
}
```

```
*******************************
* 2.1.4 Existing (OO) OMERACT-OARSI
*******************************
{
* 50% relative, 20% absolute single
* 20% relative, 10% absolute both

* Calculate Relative Change
         by id resp: gen d_rely= (d_y/y[_n-1])*100
                  * Mark Single Changes
                           by id resp: gen ex_oo_single =1 if (d_y>=20 &
d_y<.) | (d_rely>=50 & d_rely<.) & _n==2
                                    * Mark Double Changes
                                             by id resp: gen ex_oo_double
=1 if (d_y>=10 & d_y<.) | (d_rely>=20 & d_rely<.) & _n==2
                                                      * Sum double changes
                                                               by id  :
egen ex_oo_double_sum = total(ex_oo_double) if  d_y!=.

* Mark OO criteria
         by id : gen _ex_oo = cond(ex_oo_single==1 | ex_oo_double_sum==2 ,
1,0) if d_y!=.
                  by id : egen ex_oo = max(_ex_oo) if d_y!=.

                  tab ex_oo if resp==1         // Number of individuals
meeting the oo criteria
}
*******************************************************************************
***
* 2.2 Multi-level Methods
*******************************************************************************
***
// Set the global macro to identify the location and version of mlwin
global MLwiN_path "C:\Program Files (x86)\MLwiN v2.32\i386\MLwiN.exe"
         use  `simdata' , clear
                  keep if resp==1
* Create a constant
gen cons=1

******************
* 2.2.1 MLM RTN / MID Model
******************
{
*                           0-----------------1
*                           1,2,3,4,5,6,7,8,9,0,1,2,3,4,5,6,7,8,9,0,
matrix a = (1,1,1)

runmlwin y cons t if resp==1 ,
                  /// Fixed effect
         level1(t: cons, residuals(_e, )  )
/// Level 1 variance
                  level2(id: cons t, elements(a) residuals(_u, ) )
/// Level 2 varaince
                           maxiterations(10)  corr sd nopause
         //       Modelling options

* Predict Individual effects
gen xb_fe =  _b[cons] + _b[t]*t
         gen xb_re =  _u0 + _u1*t
                  gen xb = xb_fe + xb_re
```

```
* Predict to asses responsiveness at (3month)
gen xb_t =  (_b[cons]+_u0) + (_b[t]+_u1)*3

* RTN threshold
local mlm_rtn = _b[FP1:cons] + 2*(_b[RP2:var(cons)]^0.5)

* Mark RTN
gen mlm_rtn = cond(xb_t>=`mlm_rtn',1,0)

* Calculate RCI
         gen xb_d = _b[FP1:t] + _u1
                  gen se_d = (_se[FP1:t]^2 +_u1se^2)^0.5
                           gen z_d = xb_d / se_d

* Mark RCI
gen mlm_rci = cond(z_d>=1.96,1,0)

* Mark RTN RCI composite
gen mlm_rtn_rci = cond(mlm_rtn==1 & mlm_rci==1, 1, 0)
         egen pickone = tag(id)

                  tab mlm_rtn_rci if pickone==1 // Number of individuals
meeting the MLM RTN RCI  criteria
}
**********************
* 2.2.2 MLM MID
**********************
{
* MID Threshold @ 3 months
local mlm_mid = 0.5*((_b[RP2:var(t)]*3)^0.5)
         gen mlm_mid = cond( (_b[t]+_u1)*3>= `mlm_mid' ,1 ,0 )
                  tab mlm_mid if pickone==1 // Number of individuals meeting
the MLM MID criteria

* Drop previous residual and predictions
drop  _u0 _u1 _u0se _u1se _e0 _e0se  xb_fe xb_re xb xb_t xb_d se_d z_d
}
********************
* 2.2.3  MLM MCID
********************
{
* Stratify intercept and slope by satisfaction
gen consx1= cons*x1
         gen consx2 = cons*x2
                  gen tx1 = t*x1
                           gen tx2 = t*x2

* Specify RE variance matrix
*                           0-----------------1-------------------2
*                           1,2,3,4,5,6,7,8,9,0,1,2,3,4,5,6,7,8,9,0,1
matrix u = (1,1,1,0,0,1,0,0,1,1)

* Specify RE variance matrix
*                           0-----------------1-------------------2
*                           1,2,3,4,5,6,7,8,9,0,1,2,3,4,5,6,7,8,9,0,1
matrix e = (1,0,1)

runmlwin y consx1 tx1 consx2 tx2 if resp==1 ,
                                                  /// Fixed effect
```

```
          level1(t: consx1 consx2, elements(e)  residuals(_e, norecode ))
                    /// Level 1 variance
                    level2(id: consx1 tx1 consx2 tx2 ,elements(u)
residuals(_u, norecode ))    /// Level 2 varaince
                              maxiterations(10)  corr sd nopause
                                                                    //
Modelling options

* Estimate the Change  for all individuals
gen xb_slope = (_b[tx1]+_u1)*x1 + (_b[tx2]+_u3)*tx2

* Find the 75th (inverse coding 25th) centile of those satisfied
centile xb_slope if tx1==3 , c(25)
          local mlm_mcid = r(c_1)

*tag observations which have improvements greater than mcid
          gen mlm_mcid = cond(xb_slope>=`mlm_mcid',1,0) if t==3
                    tab mlm_mcid if t==3 // Number of individuals meeting the
MCID  criteria
          }
*********************
* 2.2.4  MLM (OO) OMERACT-OARSI
*********************
{
* 50% relative, 20 absolute single assuming a 0-100 score
* 20% relative, 10 absolute both assuming a 0-100 score
use  `simdata' , clear
          sort id t resp


* Create response indicators
gen cons =1
          gen consw1 = cons*w1
                    gen consw2 = cons*w2
                              gen tw1 = t*w1
                                        gen tw2 = t*w2

runmlwin y  consw1 tw1 consw2  tw2 ,
                              /// Fixed Effect
          level1(resp:)
                                                                    /// Level
1 variance
          level2(t: consw1 consw2,  residuals(_e, norecode ))
          /// Level 2 variance
                    level3(id: consw1 tw1 consw2 tw2 , residuals(_u, norecode
))        /// Level 3 varaince
                              maxiterations(10)  corr sd nopause
                                        //        Modelling options

* Calculate predicted changes
gen mlm_d = (_b[tw1] + _u1 )*tw1  + (_b[tw2] + _u3 )*tw2
          gen mlm_bl = (_b[consw1] + _u0)*consw1 + (_b[consw2] + _u2)*consw2
                    gen mlm_relyd=  (mlm_d /mlm_bl)*100

* Mark out responders
                              by id resp ,sort: gen mlm_oo_single =1 if ((
mlm_d>=20 & mlm_d<.) | (mlm_relyd>=50 & mlm_relyd<.)) & t==3
                                        * Mark Double Changes
                                                  by id resp ,sort: gen
mlm_oo_double =1 if ((mlm_d>=10 & mlm_d<.) | (mlm_relyd>=20 & mlm_relyd<.)) &
```

```
t==3
                                                        * Sum double changes
                                                                by id
,sort  : egen mlm_oo_double_sum = total(mlm_oo_double) if t==3

* Mark OO criteria
by id : gen _mlm_oo = cond(mlm_oo_single==1 | mlm_oo_double_sum==2 , 1,0) if
t==3
          by id : egen mlm_oo = max(_mlm_oo) if t==3

                    tab mlm_oo if resp==1        // Number of individuals
meeting the MLM OO criteria
}
```

BMJ Open

A unified multi-level model approach to assessing patient responsiveness including; return to normal, minimally important differences, and minimal clinical important improvement for patient reported outcome measures.

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2016-014041.R1
Article Type:	Research
Date Submitted by the Author:	21-Mar-2017
Complete List of Authors:	Sayers, Adrian; University of Bristol, Muscloskeletal Research Unit Wylde, Vikki; University of Bristol, School of Clinical Sciences Lenguerrand, Erik; University of Bristol School of Clinical Science, School of Clinical Sciences, Musculoskeletal Research Unit Gooberman-Hill, Rachael; University of Bristol, School of Clinical Sciences Dawson, Jill; University of Oxford, Department of Public Health Beard, David; University of Oxford, Nuffield Dept of Orthopaedics, Rheumatology and Musculoskeletal Sciences Price, Andrew; University of Oxford, Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences Blom, Ashley; University of Bristol, School of Clinical Sciences
Primary Subject Heading:	Research methods
Secondary Subject Heading:	Rheumatology, Epidemiology, Patient-centred medicine
Keywords:	Patient Responsiveness, Multi-level Modelling, Return To Normal, Minimal Important Difference, Patient-reported outcomes, Minimial clinical important improvement

A unified multi-level model approach to assessing patient responsiveness including; return to normal, minimally important differences, and minimal clinical important improvement for patient reported outcome measures.

Sayers A[1,2], Wylde V[1], Lenguerrand E[1], Gooberman-Hill R[1], Dawson J[3], Beard D[4], Price A[4], Blom AW[1]

Address for Correspondence

Adrian Sayers, Musculoskeletal Research Unit, School of Clinical Sciences, University of Bristol, Learning and Research Building (Level 1), Southmead Hospital, Westbury on Trym, Bristol, BS10 5NB

E-mail: adrian.sayers@bristol.ac.uk

Tel: 44 (0)117 4147880; Fax + 44(0)117 414 7924

1. Musculoskeletal Research Unit, School of Clinical Sciences, University of Bristol, Southmead Hospital, Westbury On Trym, Bristol, BS10 5NB (AS, VW, EL, RGH, AWB).
2. School of Social and Community Medicine, University of Bristol, 39 Whatley Road, Bristol, BS8 2PS.
3. Nuffield Department of Population Health, University of Oxford, Old Road Campus, Headington, Oxford OX3 7LF, UK (DB, AP).
4. Biomedical Research Unit, Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Science, Nuffield Orthopaedic Centre, Windmill Road, Oxford, OX2 9JA (JD).

Word Count 4010

Keywords: Patient Responsiveness, Multi-level Modelling, Return To Normal , Minimal Important Difference, Minimal Clinically Important Difference, Patient-reported outcomes, Clinical significance Anchor-based methods; Distribution based methods

Abstract (271 Words)

Objective

This article reviews and compares four commonly used approaches to assess patient responsiveness to a treatment or therapy [Return To Normal (RTN), Minimal Important Difference (MID), Minimal Clinically Important Improvement (MCII), OMERACT-OARSI (OO)], and demonstrates how each of the methods can be formulated in a multi-level modelling (MLM) framework.

Design

Cohort Study

Setting

A cohort of patients undergoing total hip and knee replacement were recruited from a single UK NHS hospital.

Population

400 Patients from The Arthroplasty Pain Experience (APEX) cohort study undergoing total hip (n=210) and knee (n=190) replacement who completed the Intermittent and Constant Osteoarthritis Pain (ICOAP) questionnaire prior to surgery and then at 3, 6 and 12 months after surgery.

Primary Outcomes

The primary outcome was defined as response to treatment following total hip or knee replacement. We compared baseline scores, change scores, and proportion of individuals defined as “responders” using traditional and MLM approaches to patient responsiveness.

Results

Using existing approaches, baseline and change scores are underestimated, and the variance of baseline and change scores overestimated in comparison to MLM approaches. MLM increases the proportion of individuals defined as responding in RTN, MID, and OO criteria compared to existing approaches. Using MLM with the MCII criteria reduces the number of individuals identified as responders.

Conclusion

MLM improves the estimation of the standard deviation of baseline and change scores by explicitly incorporating measurement error into the model, and avoiding regression to the mean when making individual predictions. Using refined definitions of responsiveness may lead to a reduction in misclassification when attempting to predict who does and does not respond to an intervention, and clarifies the similarities between existing methods.

Article Summary

Strengths and limitations of this study

- Four different approaches to patient responsiveness can be unified into a multi-level modelling.
- A multi-level model framework of patient responsiveness highlights the similarities and differences between existing methods.
- Multi-level models provide a simple framework which incorporates measurement error and non-linear change in trajectories of patient recovery.
- Multi-level models are technically more demanding than existing formulations of patient responsiveness, and convergence is not guaranteed.
- Multi-level models does not improve the arbitrary placement of the thresholds that define responsiveness in comparison to existing methods

INTRODUCTION

Joint replacement is an increasingly common elective procedure worldwide [1-3] and improving patient reported outcomes after joint replacement is a key research priority due to high prevalence of poor outcomes after joint arthroplasty.[4] Poor outcomes include continuing pain, functional limitations,[5] and increased healthcare utilisation.[6] However, there is some debate on how the efficacy of interventions can be judged due to the variety of different outcomes used in orthopaedic research.[7-18] Traditionally, objective primary outcomes such as prosthetic survivorship and mortality rates were used.[19] However, more recently there has been a shift in focus which ensures that patients' perspective is central to assessment of intervention success.[20] Many studies now use patient reported outcome measures (PROMs) as endpoints, and these tools can assess a variety of health outcomes, including pain,[7 21] physical functioning,[7] mental well-being[22] and health-related quality of life.[23]

Although PROMs are widely used,[4] there is still debate in how the results should be interpreted and how to define a clinically meaningful change.[24-35] From a measurement perspective, the ability to estimate if a change has occurred depends on the application of an appropriate statistical model. From a clinical perspective, some authors suggest that the average statistical change is insufficient to "tell you anything about an individual's chances of improving".[36] Therefore, the utility of simple statistical analyses are limited when attempting to help patients weigh up the risks and benefits of undergoing surgery.

In order to supplement simple statistical analysis, many researchers attempt to dichotomise the population into those who have or have not responded to an intervention, creating a two-stage process of defining an outcome. There are a number of different methods (definitions) that can be used to dichotomise the population, and these secondary analyses are collectively referred to as responsiveness analyses.[36] Four substantively different methods of estimating the proportion of individuals who respond to an intervention have been previously identified in orthopaedic

research:[36] 1) Return to Normal (RTN), 2) Distribution-based Minimally Important Difference (MID), 3) Anchor-based Minimal Clinically Important Difference (MCII), and 4) the OMERACT-OARSI (OO) responder criteria. The first three approaches are generic and used in many fields of health research, whereas the fourth approach is specific to orthopaedic research, but in principle could be used in many fields of health research.

Each of these approaches is often thought to be methodologically distinct. However, all of the methods can be shown to be special cases of a multi-level model (MLM). MLM have been used in a wide variety of contexts ranging from growth modelling to modelling educational data. One of the principal reasons to use MLM is to take advantage of the direct estimation of different variance components[37], and provide efficient and unbiased estimates of fixed and random effects.[38]

Despite a number of extensive reviews of patient responsiveness,[31 33 39 40] we will describe these four approaches to calculating responsiveness and highlight the substantively different decisions each method makes. We will then describe how each approach can be translated into a MLM framework, emphasising the benefits of the translation, and contrast the approaches using an example from the APEX cohort study.[41]

METHODS

We outline the four existing approaches to patient responsiveness previously used in orthopaedic research [36], and describe their potential limitations, and how they can formulated in a MLM framework.

Review of existing approaches to responsiveness

Return to normal (RTN)[26] suggests that an individual has returned to 'normal' if their score on a post-intervention outcome is greater than two standard deviations (SD) from the mean baseline response.

The use of two standard deviations appears to be justified on theoretical grounds, however it is quite arbitrary. Assuming scores are normally distributed and measured without error, two SD's corresponds to a 95.5% prediction interval for the mean, which is similar to the equally arbitrary and much criticised significance threshold p=0.05 (Type I error=0.05) criterion used throughout medical research[42 43]. However, there is no reason why a 1.6 or a 2.6 SD cut-offs should not be used in preference, which correspond to 90% and 99% prediction intervals.

The method also assumes the observed change is unlikely to be due to chance alone and does not account for any uncertainty. In order to alleviate this problem the use of the Relative Change Index (RCI) was proposed to be used in conjunction with the RTN classification.[24 27] The RCI constructs a test of the individual's score at follow up compared to their baseline, where the standard error of the difference is estimated indirectly using the SD of the baseline score and an assumed reliability coefficient from empirical research or a range of reliability values in the spirit of a sensitivity analysis.

A commonly described distribution-based Minimally Important Difference (MID) method classifies individuals as responders if their observed change is greater than a fixed proportion of the SD of the pre-surgery score.[30] Theve has been much debate about the exact size, or proportion, of the SD change score to use, however 0.5 SD's has been reported widely and suggested to be a difference

that is minimally perceptible to patients.[30] Any individual with a change score greater than 0.5 SD of the baseline score is defined as responding to the treatment. Similar to the RTN criteria, the decision to use 0.5 is arbitrary and there is no reason why more or less stringent criteria of 0.25, 1 or 2 SD's could not be used. Additionally, there is no reason why a test such as the RCI should not be conducted to check that change is beyond the bounds of measurement error.

Anchor-based Minimal Clinically Important Improvement (MCII) is similar to the MID approach, in that it defines an individual as a responder based on their individual change score. However, the cut-point is determined in individuals who report themselves as having an outcome which is either good/satisfactory or perceived as improved from baseline using an external anchoring question. The authors proposed using a cut point at the 75th centile of the change score, in those who are satisfied.[34] Therefore any individuals, whether they are satisfied or not, who has a change score greater than the 75th centile are defined as responders. A closely related anchor-based metric is the Patient Acceptable Symptom State (PASS),[35] the construction is similar to that of the MCII with the exception that it is based on the final score of patients opposed to change. Conceptually the PASS is more closely related to the RTN definition of responsiveness, and much of the criticism levied against MCII and RTN can therefore be applies to the PASS.

The OMERACT-OARSI (OO) criteria[32] recognises that a response to an intervention may occur in one or more different measured outcomes, i.e. a multivariate response mechanism. In keeping with much of the orthopaedic literature they assume the proposed score has been rescaled between 0 and 100 [32], and that a responder is defined as any individual with 1. a >=50% relative change or a >=20 point absolute change on one or more responses scales, or 2. a >=20% relative change or >=10 point absolute change in two or more response scales. Relative change is defined as the ratio of the change to the individual baseline score multiplied by 100. Unlike the RTN, MID, or MCII it is very clear that the thresholds for relative and absolute changes are based on a panel of expert opinions and are fixed.

Despite the variety of existing approaches used to identifying responders there are a number of problems common to all methods. Common assumptions include: 1) Each observed outcome is measured without error and reflects the true underlying patients response, test-retest reliability studies indicate that this is not a realistic assumption .[44] 2) Regression to the mean does not occur and therefore the variance of the change score will not be overestimated. 3) Floor and ceiling effects do not bias estimates of the variance of the change score.[45]

Furthermore in RTN, specific combinations of means and variances may result in a threshold beyond the range of the measurement tool, therefore no individuals would be defined as responding to a therapy. The MCII approach assumes the additional anchoring variable is measured without error and the response trajectory is distinct from those who are unsatisfied.[46] The method also assumes a two parameter logistic function is an appropriate model for the cumulative proportional rank of patients and change in outcome, and that there is no uncertainty in the calculation of the threshold .[47] Finally, the OO approach considers a response in two or more outcomes. However, it does not explicitly describe how the correlation between the two outcomes is accounted for, and fails to recognise that if not modelled appropriately may introduce bias.[48-50]

The four methods identified have a number of other limitations,[25] but they are difficult to compare methods when presented as distinct approaches.

Embedding them in a unified statistical framework makes their underlying assumptions explicit, whilst highlighting their similarities and differences. In addition, it provides a framework to incorporate non-linear change, measurement error, and variability in the timing of measurement occasions, all of which are to be expected in real word data collections and are critical when attempting to asses a patients change at a specified point in time.

Multi-level modelling approach to responsiveness

We now present a general multi-level model for patient responsiveness and show how the four approaches described above can be specified as special cases.

Under the assumption of linear change, the measured response (y) at the i^{th} occasion for the j^{th} individual is modelled as a linear function of time.

Equation 1

$$y_{ij} = \beta_0 + u_{0j} + (\beta_1 + u_{1j})t_{ij} + \varepsilon_{ij}$$

$$\begin{bmatrix} u_{0j} \\ u_{1j} \end{bmatrix} \sim N(0, \Omega_u), \qquad \Omega_u = \begin{bmatrix} \sigma^2_{u0} & \\ \sigma_{u01} & \sigma^2_{u1} \end{bmatrix}$$

$$[\varepsilon_{ij}] \sim N(0, \sigma^2_\varepsilon)$$

where t_{ij} is the time at which measurement i was taken on individual j, coded as zero at baseline. β_0 is the baseline population average response, and u_{0j} represents the j^{th} individual difference from the baseline response. The sum of $\beta_0 + u_{0j}$ is the estimated individual baseline response. β_1 represents the population average change per unit increase in time , and u_{1j} represents the j^{th} individual difference from the population average change per unit increase in time. The sum of $\beta_1 + u_{1j}$ is the estimated individual average change per unit increase in time. Measurement error in the linear trajectory is represented by ε_{ij}.

The variance in individual deviations from the population average response at baseline and average rate of change are σ^2_{u0} and σ^2_{u1} respectively. Furthermore, the correlation between baseline measurements and rate of change can be assumed to be independent or correlated by constraining σ_{u01} to be zero or allowing it to be freely estimated. The variances of the shrunken residuals $\hat{u}_{0j}$ and $\hat{u}_{1j}$, also known as empirical bayes estimates, are typically less than the estimated population variances $\hat{\sigma}^2_{u0}$ and $\hat{\sigma}^2_{u1}$ as they shrink towards the population averages of β_0 and β_1 . The extent of the shrinkage depends on the number of measurement occasions and the within individual

variability, with greater shrinkage as the number of measurement occasions decrease and as the within individual variance increases. A more detailed discussion of MLM can be found in most advanced statistics textbooks.[48 51 52]

We now describe how the four traditional approaches to measuring patient responsiveness can be unified into a MLM framework. General benefits of the MLM over existing approaches include: 1) with more than three measurement occasions a MLM directly allows for measurement error, ε_{ij} ; 2) the use of shrunken residuals $\widehat{u_{0j}}$ and $\widehat{u_{1j}}$ allow for regression to the mean when predicting an individual's score [53]; 3) MLM can be extended to include multivariate response models which appropriately model the correlation between two or more outcomes; and 4) MLM allows for variability in the timing of measurement occasions. Fundamentally, the MLM approach recognises that observed patient responses are subject to error, and therefore the true patient's response following an intervention must be estimated.

MLM-Return To Normal. In order to apply the RTN criteria using a MLM approach we first estimate the baseline population SD in individuals considered to be abnormal using the model described in Equation 1. Assuming y_{ij} is normally distributed at baseline with a population mean β_0 and variance σ_{u0}^2 a $100 \cdot \left(1 - \frac{\alpha}{2}\right)$ prediction interval for the baseline measurement can be constructed i.e. $\left[\beta_0 - \sigma_{u0}\mathrm{z}_{\left(1-\frac{\alpha}{2}\right)}, \beta_0 + \sigma_{u0}\mathrm{z}_{\left(1-\frac{\alpha}{2}\right)}\right]$ where α is the type I error rate and z is the critical value from a standard normal distribution. Importantly y_{ij} is not assumed to be measured without error and therefore estimates of σ_{u0}^2 are less likely to be biased than using simple methods. However, it is important to note that the choice of α is entirely that of the researcher, and whilst α =0.05 (leading to $z = 1.96 \approx 2$) is common, more or less stringent criteria could be applied.

The second step is to estimate the score of the individual at time *j* following surgery and determine if it is within the baseline prediction interval. This prediction is simply calculated by substituting

estimates of β_0 , β_1 , u_{0j} and u_{1j} into Equation 1, to give the empirical best linear unbiased prediction (eBLUP) for the j^{th} individual at the i^{th} occasion.[54]

Finally, in order to determine whether or not the response of the individual following surgery is greater than one would attribute to chance alone, i.e. the null hypothesis that the j^{th} individuals slope is not equal to zero, a test statistic similar to RCI should be conducted,

$(\hat{\beta}_1 + \hat{u}_{1j})/SE(\hat{\beta}_1 + \hat{u}_{1j})$, where $SE(\hat{\beta}_1 + \hat{u}_{1j}) = \sqrt{VAR(\hat{\beta}_1) + VAR(\hat{u}_{1j})}$.

MLM-Minimally Important Difference. The threshold of minimally important difference can also be estimated using a MLM. Similar to RTN, a linear model of change is applied, as in Equation 1. Then the population SD of the baseline response is estimated by σ_{u0}. By comparing the estimated change for the j^{th} individual $(\hat{\beta}_1 + \hat{u}_{1j})t$ to the baseline standard deviation, i.e. $\sigma_{u0}/2$, the individual can be classed as a responder or not. The MID approach does not specifically state whether a test of whether an individual's change scores is less than the MID threshold should be conducted, but a test statistic is simply constructed as $\left((\hat{\beta}_1 + \hat{u}_{1j})t - \left(\frac{\hat{\sigma}_{u0}}{2}\right)\right) \Big/ (SE(\hat{\beta}_1 + \hat{u}_{1j})t)$.

MLM-Minimally Clinically Important Improvement. The MLM MCII requires a simple extension of the univariate model presented previously (Equation 1). The outcome of interest is stratified using an external criterion. The stratification is achieved by creating dummy variables for those who are un/satisfied with some aspect of their treatment i.e. x_{1i} takes the values 0 and 1 representing unsatisfied and satisfied individuals respectively, and $x_{2i} = 1 - x_{1i}$. These dummy variables are then included as additional explanatory variables, with no overall model intercept, and interacted with *t.*

Equation 2

$$y_{ij} = (\beta_0 + u_{0j})x_{1i} + (\beta_1 + u_{1j})t_{ij}x_{1i} + \varepsilon_{1ij}x_{1i}$$

$$+ (\beta_2 + u_{2j})x_{2i} + (\beta_3 + u_{3j})t_{ij}x_{2i} + \varepsilon_{2ij}x_{2i}$$

$$\begin{bmatrix} u_{0j} \\ u_{1j} \\ u_{2j} \\ u_{3j} \end{bmatrix} \sim N(0, \Omega_u): \qquad \Omega_u = \begin{bmatrix} \sigma^2_{u0} & & & \\ \sigma_{u01} & \sigma^2_{u1} & & \\ 0 & 0 & \sigma^2_{u2} & \\ 0 & 0 & \sigma_{u23} & \sigma^2_{u3} \end{bmatrix}$$

$$\begin{bmatrix} \varepsilon_{1ij} \\ \varepsilon_{2ij} \end{bmatrix} \sim N(0, \Omega_\varepsilon): \qquad \Omega_\varepsilon = \begin{bmatrix} \sigma^2_{\varepsilon 1} & \\ 0 & \sigma^2_{\varepsilon 2} \end{bmatrix}$$

Therefore β_0 and β_2 are the mean population outcome score at baseline for those who are satisfied and unsatisfied respectively, and β_1 and β_3 are the corresponding mean population changes per unit of time. Variances and covariances are similarly interpreted for those who are satisfied and unsatisfied respectively. However, that satisfaction on the external anchoring question is assumed to be known without error, and individual effects and errors for x_{1i} are uncorrelated with those for x_{2i} because the satisfied and unsatisfied categories are mutually exclusive. Whether or not it is desirable to fit a model to both satisfied and unsatisfied individuals simultaneously is debateable, as only those who are satisfied contribute to the definition of MCII. However, we present a simultaneous modelling approach to satisfied and unsatisfied individuals as it make the underlying modelling assumptions explicit. Furthermore, if the stratification on satisfaction status leads to a small samples alternative estimators and degree of freedom can be used in a MLM framework to account for this i.e. restricted maximum likelihood, restricted generalised least squares, or adjustments to the denominator degrees of freedom.[55]

Following prediction of each individual's trajectory, including those unsatisfied with treatment, the second stage in the MCII method requires a threshold for determining responsiveness. Using a similar suggestion to Tubach et al.,[35] the 75th centile of those who are satisfied could be used to classify all individuals as responding or not. Similar to the MID there is no suggestion of whether a

test against the null value of the 75th centile should be constructed, but this is easily done within the MLM framework.

MLM-OMERACT-OARSI criteria. The OO criteria can be similarly extended into a multi-variate MLM framework by the inclusion of dummy variables and reshaping into a "double" long format with both responses stored in a single vector. Figure 1 illustrates the data structure for a bivariate model.

Dummy variables, also known as response indicators, are used to denote the response options: w_{1i} is coded 1 for the first measurement outcome (pain) and 0 for the second outcome (function), and $w_{2i} = 1 - w_{1i}$. The response indicators and their interactions with t are included as explanatory variables to obtain the following bivariate response model.

Equation 3

$$y_{ij} = (\beta_0 + u_{0j})w_{1i} + (\beta_1 + u_{1j})t_{ij}w_{1i} + \varepsilon_{1ij}w_{1i}$$

$$+ (\beta_2 + u_{2j})w_{2i} + (\beta_3 + u_{3j})t_{ij}w_{2i} + \varepsilon_{2ij}w_{2i}$$

$$\begin{bmatrix} u_{0j} \\ u_{1j} \\ u_{2j} \\ u_{3j} \end{bmatrix} \sim N(0, \Omega_u): \qquad \Omega_u = \begin{bmatrix} \sigma_{u0}^2 & & & \\ \sigma_{u01} & \sigma_{u1}^2 & & \\ \sigma_{u02} & \sigma_{u12} & \sigma_{u2}^2 & \\ \sigma_{u03} & \sigma_{u13} & \sigma_{u23} & \sigma_{u3}^2 \end{bmatrix}$$

$$\begin{bmatrix} \varepsilon_{1ij} \\ \varepsilon_{2ij} \end{bmatrix} \sim N(0, \Omega_\varepsilon): \qquad \Omega_\varepsilon = \begin{bmatrix} \sigma_{\varepsilon 1}^2 & \\ \sigma_{\varepsilon 12} & \sigma_{\varepsilon 2}^2 \end{bmatrix}$$

With a similar functional form to the univariate MLM, there are separate population and individual intercepts for the first and second outcome (β_0 , β_2 and u_{0j}, u_{2j} respectively), and separate population and individual slopes are estimated for the second outcome $(\beta_1$, β_3 and $u_{1j}, u_{3j})$. Using a MLM approach the outcomes are modelled jointly, which allows for non-zero covariances

between the intercepts and slopes of the two responses ($\sigma_{u02}, \sigma_{u12}, \sigma_{u03}, \sigma_{u13}$). The measurement errors for the two responses are not assumed to be independent, with their covariance directly estimated ($\sigma_{\varepsilon 12}$).

Finally, the threshold of response must be decided and individual trajectories estimated and classified. Similar to the other methods it is relatively simple to construct a test statistic for testing whether individual slopes are significantly different from the chosen threshold.

Limitations of the MLM approach. The MLM approach described by Equation 1, Equation 2 and 3 assumes that change in the outcome is linearly associated with time. The linearity assumption is imposed for simplicity. Non-linear changes are easily incorporated by including higher order polynomials or using linear or non-linear splines.[56]

The standard MLM approach also fails to directly address the issue of floor and ceiling effects. Mixed response multi-level tobit models allow for such effects and provide some adjustment.[45 57] Furthermore, whilst the MLM described in Equation 2 allow for heterogeneity in known groups, they fail to allow for heterogeneity in trajectories when the groups are unknown. The use of group based trajectory models or growth mixture models in these circumstances may reveal latent (unobserved) classes of individuals with distinct patterns of recovery.[58]

Example: The APEX cohort Study

Using a mixed cohort of patients undergoing THR and TKR, [41] we investigated the performance of the existing and MLM approaches using four definitions of responsiveness. A simulated dataset and code to fit each of these models is included in supplementary material.

Patients in the APEX cohort completed the Intermittent and Constant Osteoarthritis Pain (ICOAP) questionnaire before and after surgery at approximately 0, 3, 6 and 12 months. The date at which the post-surgical questionnaire was completed is recorded in days post-surgery. As the name suggests, the ICOAP questionnaire attempts to measure intermittent and constant pain. [21] The developers of the tool suggest three ways of summarising the scale to generate an intermittent, constant and total pain scores (the sum of the intermittent and constant pain subscales). The tool is scored between 0 and 100 and a full description of the ICOAP scale is provided in the original validation paper.[21] Satisfaction of pain relief following surgery was recorded by asking patients to "Rate of Relief provided by (hip/knee) replacement?" using a single item 5 point scale (None, Poor, Fair, Good, Excellent), we categorised good and excellent as a satisfactory outcome following surgery.

Using the three methods of aggregation, we present estimates of pain at baseline and for change at approximately 3 months post-surgery using existing methods (summary statistics) and MLM estimates.

In order to facilitate comparisons between existing and MLM approaches we assume that all individuals are measured at exactly 0, 3, 6, and 12 months. Whilst the existing approaches only utilises the 0 and 3 month measurements the MLM approach uses a random intercept and random slopes across 4 measurements occasions, using two linear splines with a knot point at 3 months to estimate the response at 3 months. The inclusion of the second spline and the additional two measurement occasions allows adjustment for measurement error in the MLM approach. Table 1

and 2 presents results for patients undergoing THR and TKR respectively. The placement of the knot at 3 months was determined by visually inspecting the data, similar to the methods by Lenguerrand et al.[59] With more complex patterns of response an iterative model fitting approach is likely to be required to determine the optimal knot placement. Modelling assumptions were checked using ladder plots, and normal plots of residuals.

To describe how the responsiveness classification in patients changed at 3 months, we used an Exact McNemar test to compare the number of discordant classifications generated by existing and MLM approaches.

The APEX study were approved by Southampton and South West Hampshire Research Ethics Committee (09/H0504/94).

RESULTS

In all subdivisions of the ICOAP questionnaire, for THR/TKR patients, the estimates of the baseline mean and change scores are approximately equal to those from the MLM approaches. In addition, estimates of the SD of baseline and change score are overestimated using existing approaches in THR/TKR patients. The SD of baseline measurements is approximately 3.3 and 3.75 points greater in existing methods in THR/TKR patients respectively, while the corresponding SD of change scores are approximately 6.3 and 7 points greater in existing methods, see table 1 and 2 respectively. An example of model diagnostics is included in Figure 2, which presents the observed ICOAP total scores at 0, 3, 6, and 12 months and the population average response in ICOAP across time. In addition, baseline, change residuals are also presented using quantile quantile plots.

Table 1: Mean and standard deviation of baseline and change scores estimated using current and multi-level model approaches to responsiveness in patient undergoing total hip replacement in the APEX cohort study. Betas represent the population average characteristic and sigma the estimated standard deviation. Baseline is assumed to be the day of surgery, and change is from 0 to 3.6 months.

			Current Approaches to Responsiveness				Multi-Level Model Approaches to Responsiveness			
		N	Baseline β_0 σ_{u0}	Change β_1 σ_{u1}	Absolute Threshold	P(Resp.)	Baseline β_0 σ_{u0}	Change β_1 σ_{u1}	Absolute Threshold	P(Resp.)
Return to Normal	Total Pain	210	43.71 (22.1)	45.76 (24.0)	87.9	70.5 (63.8, 76.6)	43.71 (20.1)	46.14 (19.7)	83.8	78.1 (71.9, 83.5)
MID		210			11.0	91.9 (87.4, 95.2)			10.0	97.6 (94.5, 99.2)
MCID (Satisfied)		185	44.37 (22.0)	48.43 (22.6)	32.6	71.9 (65.3, 77.9)	44.37 (20.3)	48.54 (19.2)	35.8	67.1 (74.5, 85.6)
MCID (UnSatisfied)		25	38.77 (22.4)	26.05 (25.4)			38.77 (17.0)	28.43 (16.3)		
Return to Normal	Chronic Pain	210	49.19 (27.2)	44.23 (27.3)	103.5	0 (0, 1.7)	49.19 (25.6)	44.35 (24.0)	100.3	0 (0, 1.7)
MID		210			13.6	84.3 (78.6, 88.9)			12.8	88.6 (83.5, 92.5)
MCID (Satisfied)		185	50.08 (27.4)	46.37 (26.7)	30.0	72.4 (65.8, 78.3)	50.08 (26.3)	46.21 (24.5)	31.0	73.3 (44.2, 58.9)
MCID (UnSatisfied)		25	42.60 (24.8)	28.40 (26.9)			42.60 (18.3)	30.60 (12.6)		
OO		210	49.19 (27.2)	44.23 (27.3)	20(10)	92.4 (87.9, 95.6)	49.19 (25.3)	44.35 (23.4)	20(10)	99.5 (54.8, 69)
Return to Normal	Intermittent Pain	210	39.13 (21.7)	47.06 (26.5)	82.5	70 (63.3, 76.1)	39.13 (18.7)	47.66 (20.5)	76.5	80.5 (90.5, 97.4)
MID		210			10.8	90 (85.1, 93.7)			9.3	97.1 (30, 44.1)
MCID (Satisfied)		185	39.60 (21.7)	50.17 (24.9)	37.5	71.4 (64.8, 77.4)	39.60 (19.2)	50.50 (19.1)	40.5	67.1 (84.8, 93.9)
MCID (UnSatisfied)		25	35.58 (21.4)	24.08 (26.6)			35.58 (13.9)	26.69 (17.1)		
OO		210	39.13 (21.7)	47.06 (26.5)	20(10)	92.4 (87.9, 95.6)	39.13 (18.5)	47.66 (19.1)	20(10)	99.5 (60.3, 73.5)

MID = Minimally Important Difference, MCID = Minimally Clinically Important Difference, OO= OMERACT OARSI responder criteria. P(Resp.) = Proportion of Responders.

Table 2: Mean and standard deviation of baseline and change scores estimated using current and multi-level model approaches to responsiveness in patient undergoing total knee replacement in the APEX cohort study. Betas represent the population average characteristic and sigma the estimated standard deviation. Baseline is assumed to be the day of surgery, and change is from 0 to 3.6 months.

			Current Approaches to Responsiveness				Multi-Level Model Approaches to Responsiveness			
		N	Baseline β_0 σ_{u0}	Change β_1 σ_{u1}	Absolute Threshold	P(Resp.)	Baseline β_0 σ_{u0}	Change β_1 σ_{u1}	Absolute Threshold	P(Resp.)
Return to Normal	Total Pain	190	42.86 (19.7)	31.27 (23.2)	82.3	43.2 (36, 50.5)	42.89 (16.7)	32.09 (17.7)	76.3	51.6 (60.3, 73.5)
MID		190			9.9	79.5 (73, 85)			8.3	93.2 (60.3, 73.5)
MCID (Satisfied)		138	44.09 (19.7)	38.51 (20.6)	22.7	62.6 (55.3, 69.5)	44.13 (16.7)	38.76 (14.7)	29.9	55.3 (66.8, 79.2)
MCID (UnSatisfied)		52	39.62 (19.7)	12.04 (18.0)			39.62 (16.3)	14.28 (11.5)		
Return to Normal	Chronic Pain	190	47.76 (23.6)	31.61 (25.5)	94.9	44.7 (37.5, 52.1)	47.79 (20.5)	32.46 (19.5)	88.7	36.8 (47.9, 62.5)
MID		190			11.8	74.7 (67.9, 80.7)			10.2	90 (47.9, 62.5)
MCID (Satisfied)		138	48.80 (23.4)	38.59 (23.3)	23.7	64.2 (57, 71)	48.88 (20.5)	38.88 (17.7)	30.3	55.3 (47.4, 62)
MCID (UnSatisfied)		52	45.00 (24.1)	13.08 (21.9)			45.00 (20.1)	15.26 (13.3)		
OO		190	47.76 (23.6)	31.61 (25.5)	20(10)	81.0 (74.7, 86.3)	47.78 (20.2)	32.50 (18.9)	20(10)	98.4 (47.9, 62.5)
Return to Normal	Intermittent Pain	190	38.78 (18.2)	30.97 (23.9)	75.3	40.5 (33.5, 47.9)	38.80 (13.8)	31.77 (16.7)	66.4	62.1 (47.9, 62.5)
MID		190			9.1	78.9 (72.5, 84.5)			6.9	94.7 (97.4, 100)
MCID (Satisfied)		138	40.15 (18.3)	38.45 (21.2)	24.8	61.6 (54.3, 68.5)	40.20 (14.1)	38.63 (12.8)	31.2	54.7 (97.4, 100)
MCID (UnSatisfied)		52	35.14 (17.8)	11.12 (19.0)			35.14 (12.8)	13.40 (10.8)		
OO		190	38.78 (18.2)	30.97 (23.9)	20(10)	81.0 (74.7, 86.3)	38.81 (13.6)	31.74 (15.7)	20(10)	98.4 (95.5, 99.7)

MID = Minimally Important Difference, MCID = Minimally Clinically Important Difference, OO= OMERACT OARSI responder criteria. P(Resp.) = Proportion of Responders.

Return To Normal

Using similar baseline score estimates to the conventional RTN approach and different SD's results in a reduction in the threshold of response by approximately 5 points in THR/TKR patients. The change in threshold is due to smaller estimates of baseline and change SD's. When considering the total ICOAP score, the MLM approach classifies approximately 10% more individuals as responders than existing approaches. It is also interesting to note that the threshold of response using the existing approach when considering total ICOAP score in THR patients is beyond the range of the score.

Minimally Important Difference

Using similar change score estimates and different SD's results in an approximately 2 point reduction in the MID threshold in THR/TKR patients. The reduced threshold results in more individuals being classified as responders using the MLM approach.

Minimally Clinically Important Difference

Using the MLM approach in satisfied and unsatisfied individuals results in a small increase in the threshold of response in comparison to existing approaches. The increase in threshold is due to shrunken residuals and therefore reduced variability of predicted change scores. The increase in threshold results in a reduced number of individuals (3% of THR patients and 6% of TKR patients) being identified as responders.

OMERACT-OARSI

The OO approach uses fixed definitions of responsiveness. Individual estimates of change from the bivariate MLM for constant and intermittent pain are very similar to those from the univariate MLM. However the standard deviation of the change score is reduced by approximately 0.5 and 1 points in constant and intermittent pain comparing the univariate and bivariate MLM respectively, whereas

the SD of baseline score approximately the same. Despite the larger absolute threshold of 20 and 10 points for changes in 1 or 2 items respectively, i.e. larger than MID, there is an increase in the proportion of individuals identified as responding. The increase is partly due to the use of the relative change threshold, and the reduced variability in change in comparison to the univariate MLM using MID definition of responsiveness.

Responsiveness Classification

The effect of using a MLM approach to define patient responsiveness compared to existing approaches is presented in Tables 3 and 4 for THR and TKR patients respectively. Whilst the use of MLM provides refined thresholds of responsiveness it fundamentally changes the way individuals are classified due to adjustment for measurement error, regression to the mean and ability to conduct refined test. Patients previously defined as non-responding using existing methods are now responders (Positive change) in MLM approaches, and similarly patients defined as responders using existing methods are classified as non-responders (negative change) in MLM, see Figure 3 for graphical illustration. MLM MID and OO methods appear to be most consistent in the reclassification of patients increasing the number of patients defined as non-responders using existing methods as responders in MLM approaches. Whereas MLM RTN and MCII provide a more fundamental change the classifications of patient responsiveness.

Table 3: Cross classification of responsiveness status in THR patients using existing and MLM model approaches to responsiveness: Return To Normal (RTN), Minimally Important Difference (MID), Minimally Clinical Important Improvement (MCII), and OMERACT OARSI (OO) Criteria.

Total Hip Replacement ICOAP			Multilevel Model							
			RTN		MID		MCII		OO	
			N.Resp	Resp	N.Resp	Resp	N.Resp	Resp	N.Resp	Resp
Existing	Total	N.Resp	**36**	**26**	**5**	**12**	**52**	**7**	-	-
		Resp	**10**	**138**	**0**	**193**	**17**	**134**	-	-
	Chronic	N.Resp	210	0	**24**	**9**	52	6	-	-
		Resp	0	0	**0**	**177**	4	148	-	-
	Intermittent	N.Resp	**33**	**30**	**6**	**15**	50	10	-	-
		Resp	**8**	**139**	**0**	**189**	19	131	-	-
	Chronic & Intermittent	N.Resp	**-**	**-**	**-**	**-**	-	-	**1**	**15**
		Resp	**-**	**-**	**-**	**-**	-	-	**0**	**194**

N.Resp= Non-Responders; Resp = Responders; Bold Cells indicate significance (p<=0.05) of discordant pairs using Exact McNemar test.

Table 4: Cross classification of responsiveness status in TKR patients using existing and MLM model approaches to responsiveness: Return To Normal (RTN), Minimally Important Difference (MID), Minimally Clinical Important Improvement (MCII), and OMERACT OARSI (OO) Criteria.

Total Knee Replacement ICOAP			Multilevel Model							
			RTN		MID		MCII		OO	
			N.Resp	Resp	N.Resp	Resp	N.Resp	Resp	N.Resp	Resp
Existing	Total	N.Resp	**81**	**27**	**13**	**26**	**64**	**7**	-	-
		Resp	**11**	**71**	**0**	**151**	**21**	**98**	-	-
	Chronic	N.Resp	92	13	**19**	**29**	61	7	-	-
		Resp	28	57	**0**	**142**	24	98	-	-
	Intermittent	N.Resp	**69**	**44**	**9**	**31**	63	10	-	-
		Resp	**3**	**74**	**1**	**149**	23	94	-	-
	Chronic & Intermittent	N.Resp	**-**	**-**	**-**	**-**	-	-	**3**	**33**
		Resp	**-**	**-**	**-**	**-**	-	-	**0**	**154**

N.Resp= Non-Responders; Resp = Responders; Bold Cells indicate significance (p<=0.05) of discordant pairs using Exact McNemar test.

DISCUSSION

The primary purpose of a responsiveness analysis is to convey the variability of an individual's chances of perceiving an improvement following a treatment. Existing approaches appear to be distinct from one another, and the precise relationship between existing methods were unclear.

We have clearly shown how four commonly used approaches to estimating patient responsiveness can be incorporated into the unified statistical framework of MLM. There translation in to unified framework makes many of the assumption (linearity of response, heterogeneity in timing of measures, multiple measurements) underpinning existing approaches clear. The application of patient responsiveness models in a cohort of orthopaedic patients illustrates how SD's of baseline and change scores in existing approaches are overestimated in comparison to the MLM approach. Thresholds for defining responders from MLM are lower when based on SD, and therefore existing approaches to RTN & MID may appear to provide a worse case scenario with regards the efficacy of a treatment or therapy. Similarly, responsiveness approaches based on the distribution of predicted change scores (MCII) are higher in MLM, and therefore existing thresholds could be described as a best case scenario in comparison to existing approaches. However, the reclassification of patients using the MLM is more fundamental than increasing or reducing the threshold to determine responsiveness, the implicit adjustments for measurement error and regression to the mean change which patients are defined as responding or not.

MLM are not the panacea of patient responsiveness methods, however they do highlight implicit assumptions in existing approaches and provide sensible adjustments for measurement error, regression to the mean and heterogeneity in the timing of measurements in clinical studies.

From a clinical perspective, it is very clear there are differences in the outcomes at 3 months following THR and TKR. Whilst patient's baseline level of pain, are similar between THR and TKR, the response to surgery is less, and consistently less (lower variability) for all pain domains. Similarly, we

have previously observed different patterns of pain, in relation to pain at rest and pain on movement,[60] yet the mechanisms underpinning theses effects are unclear and require more research, but this does emphasize the necessity to treat hip and knee osteoarthritis as separate disease states.

Strengths & Limitations

One of the key benefits of adopting a MLM approach when defining clinically meaningful change is the improved estimation of individual change by the greater flexibility in the MLM framework. Specifically, MLM do not assume the response is measured without error, they adjust for regression to the mean, the trajectory of recovery is not constrained to be linear, and data from multiple measurements and variability in the timing of those measurement occasions can also be incorporated into the model. Furthermore, assuming the underlying MLM adequately represents the true causal mechanism, parameter estimates, SD's and standard errors will be unbiased in comparison to existing approaches.

Furthermore, the unification of existing approaches into a MLM framework clearly shows the relationship between the four different approaches. For example, RTN and MID share the same underlying model. MCII is also the same at RTN/MID if you assume the baseline and change scores are the same across strata of un/satisfied patients. Similarly, the model underlying OO approach is the same as the RTN/MID approach if you assume independence in the measured outcomes of the two trajectories, and error term.

Despite the numerous benefits of adopting a MLM approach, it is not to say it is without some limitations. MLM are technically more demanding than existing formulations of patient responsiveness, and whilst there are no theoretical limits on how large or small samples have to be, model convergence is not guaranteed, and the need to use appropriate estimation methods[38] or denominator degrees of freedom[55] when calculating standard errors requires consideration.

Furthermore, it is important to perform model diagnostic to check the data fit with the model. MLM does not improve the arbitrary placement of the thresholds that define responsiveness in comparison to existing methods, and despite the improved trajectory modelling it is currently unclear if the refined definitions correlate more strongly with patient expectations, functional data, long term self-reported outcomes, or hard end-points such as mortality and revision. Further research externally validating the classification using patient groups, expert opinion[61] or functional data may demonstrate improved classification of those responding to treatment in comparison to existing methods.

It is clear the MLMs provide considerable advantages over existing approaches to identifying patients who respond to a treatment. Consequently, the proportion of individuals thought not to be responding to treatment may be smaller than previously thought. Using the redefined definition may reduce the number of individuals misclassified as non-responders, and improve the prediction of those individuals who are likely to respond to treatment.

Figures

Figure 1: Illustration of a “double” long data setup for creating a bivariate MLM.

Figure 2: Modelling diagnostic plots. Upper left, ladder plot of observed ICOAP total scores at 0, 3, 6, and 12 months following THR, and population average trajectory estimated from a MLM, used in RTN and MID analysis, with 2 linear splines with a knot at 3 months. Upper right, lower left and right plots are quantile-quantile plots of the residual distribution of random effects estimated from a MLM with 2 linear splines with a knot at 3 months.

Figure 3: Change in Responder classification using a RTN definition comparing existing approaches to MLM approach using the ICOAP total score in patients following THR. Upper Left panel illustrates observed trajectories for patients whose responsiveness classification changes using a MLM approach to estimating responsiveness. Lower left panel illustrates the observed and predicted trajectories of ICOAP total score in patients positively reclassified as responders compared to existing approaches. Lower right panel illustrates the observed and predicted trajectories of ICOAP total score in patients negatively reclassified as non-responders compared to existing approaches.

Abbreviations

APEX – Arthroplasty Pain Experience

ICOAP - Intermittent and Constant Osteoarthritis Pain

MCII – Minimally Clinical Important Improvement

MID – Minimal Important Difference

MLM – Multi Level Model

OO – OMERACT OARSI Criteria

RCI – Relative Change Index

RTN – Return To Normal

SD – Standard Deviation

SE – Standard Error

THR – Total Hip Replacement

TKR – Total Knee Replacement

Acknowledgements

We would like to thank Professor Fiona Steele for her extensive comments and help preparing this manuscript.

Author Contributions

Study Conception (AS). APEX study design (VW, RGH, AWB). APEX acquisition of data (VW, RGH, AWB, EL). ACHE study design (JD, DB, AP). Wrote first draft & revised manuscript (AS). Drafting and review of manuscript (AS, VW, RGH, AWB, EL, JD, DB, AP). Final approval of Manuscript (AS, VW, RGH, AWB, EL, JD, DB, AP)

Funding Statement

This work was supported by AS is funded by an MRC Fellowship MR/L01226X/1 and HTA Project:11/63/01 – 'ACHE'. This article presents independent research funded by the National Institute for Health Research (NIHR) under its Programme Grants for Applied Research programme (RP-PG-0407-10070). The views expressed in this article are those of the authors and not necessarily those of the NHS, the NIHR or the Department of Health. The research team acknowledge the support of the NIHR, through the Comprehensive Clinical Research Network.

Competing Interest

The Authors have no competing interests to declare.

Data Sharing

No data is available to be shared.

REFERENCES

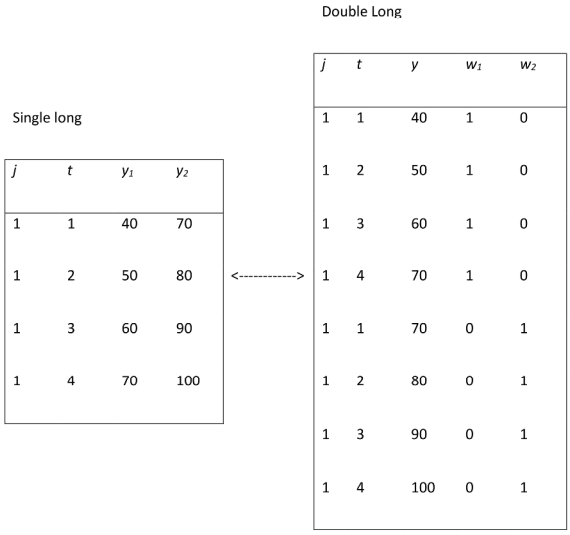
1. Felson DT, Naimark A, Anderson J, et al. The prevalence of knee osteoarthritis in the elderly. The Framingham Osteoarthritis Study. *Arthritis and rheumatism* 1987;30(8):914-8. [published Online First: 1987/08/01]
2. Lawrence RC, Felson DT, Helmick CG, et al. Estimates of the prevalence of arthritis and other rheumatic conditions in the United States. Part II. *Arthritis and rheumatism* 2008;58(1):26-35. doi: 10.1002/art.23176
3. National Joint Registry. 10th Annual Report 2013. Hemel Hempstead2013.
4. Beswick AD, Wylde V, Gooberman-Hill R, et al. What proportion of patients report long-term pain after total hip or knee replacement for osteoarthritis? A systematic review of prospective studies in unselected patients. *Bmj Open* 2012;2(1) doi: ARTN e000435

DOI 10.1136/bmjopen-2011-000435
5. Jeffery AE, Wylde V, Blom AW, et al. "It's there and I'm stuck with it": patients' experiences of chronic pain following total knee replacement surgery. *Arthritis care & research* 2011;63(2):286-92. doi: 10.1002/acr.20360
6. Kassam A, Dieppe P, Toms AD. An analysis of time and money spent on investigating painful Total Knee Replacements. *British Journal of Medical Practitioners* 2012;5(3)
7. Bellamy N, Buchanan WW, Goldsmith CH, et al. Validation study of WOMAC: a health status instrument for measuring clinically important patient relevant outcomes to antirheumatic drug therapy in patients with osteoarthritis of the hip or knee. *The Journal of rheumatology* 1988;15(12):1833-40.
8. Klassbo M, Larsson E, Mannevik E. Hip disability and osteoarthritis outcome score. An extension of the Western Ontario and McMaster Universities Osteoarthritis Index. *Scandinavian journal of rheumatology* 2003;32(1):46-51.
9. Roos EM, Roos HP, Lohmander LS, et al. Knee Injury and Osteoarthritis Outcome Score (KOOS)--development of a self-administered outcome measure. *The Journal of orthopaedic and sports physical therapy* 1998;28(2):88-96. doi: 10.2519/jospt.1998.28.2.88
10. Dawson J, Fitzpatrick R, Carr A, et al. Questionnaire on the perceptions of patients about total hip replacement. *J Bone Joint Surg Br* 1996;78B(2):185-90.
11. Dawson J, Fitzpatrick R, Murray D, et al. Questionnaire on the perceptions of patients about total knee replacement. *J Bone Joint Surg Br* 1998;80B(1):63-69. doi: Doi 10.1302/0301-620x.80b1.7859
12. Focht BC, Rejeski WJ, Ambrosius WT, et al. Exercise, self-efficacy, and mobility performance in overweight and obese older adults with knee osteoarthritis. *Arthritis and rheumatism* 2005;53(5):659-65. doi: 10.1002/art.21466
13. Smith AJ, Dieppe P, Howard PW, et al. Failure rates of metal-on-metal hip resurfacings: analysis of data from the National Joint Registry for England and Wales. *Lancet* 2012;380(9855):1759-66. doi: 10.1016/s0140-6736(12)60989-1
14. Smith AJ, Dieppe P, Porter M, et al. Risk of cancer in first seven years after metal-on-metal hip replacement compared with other bearings and general population: linkage study between the National Joint Registry of England and Wales and hospital episode statistics. *Bmj* 2012;344:e2383. doi: 10.1136/bmj.e2383
15. Hunt LP, Ben-Shlomo Y, Clark EM, et al. 45-day mortality after 467 779 knee replacements for osteoarthritis from the National Joint Registry for England and Wales: an observational study. *Lancet* 2014 doi: 10.1016/s0140-6736(14)60540-7

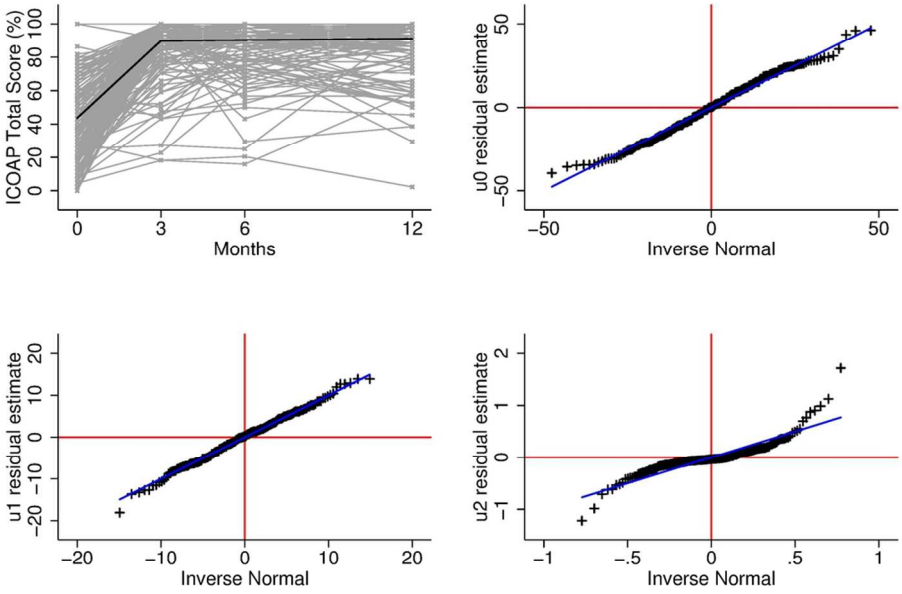
16. Hunt LP, Ben-Shlomo Y, Clark EM, et al. 90-day mortality after 409,096 total hip replacements for osteoarthritis, from the National Joint Registry for England and Wales: a retrospective analysis. *Lancet* 2013;382(9898):1097-104. doi: 10.1016/s0140-6736(13)61749-3
17. Riddle DL, Stratford PW, Bowman DH. Findings of extensive variation in the types of outcome measures used in hip and knee replacement clinical trials: A systematic review. *Arthrit Rheum-Arthr* 2008;59(6):876-83. doi: Doi 10.1002/Art.23706
18. Wylde V, Bruce J, Beswick A, et al. Assessment of chronic postsurgical pain after knee replacement: a systematic review. *Arthritis care & research* 2013;65(11):1795-803. doi: 10.1002/acr.22050
19. Wylde V, Blom AW. The failure of survivorship. *The Journal of bone and joint surgery British volume* 2011;93(5):569-70. doi: 10.1302/0301-620X.93B5.26687 [published Online First: 2011/04/23]
20. Darzi. High quality care for all: NHS Next Stage Review final report, 2008.
21. Hawker GA, Davis AM, French MR, et al. Development and preliminary psychometric testing of a new OA pain measure--an OARSI/OMERACT initiative. *Osteoarthritis and cartilage / OARS, Osteoarthritis Research Society* 2008;16(4):409-14. doi: 10.1016/j.joca.2007.12.015
22. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. *Acta Psychiatr Scand* 1983;67(6):361-70.
23. Williams A, Kind P. The present state of play about QALYs. In: Hopkins A, ed. Measure of the quality of life: the uses to which they may be put: RCP publications 1992.
24. Christensen L, Mendoza JL. A Method of Assessing Change in a Single Subject - an Alteration of the Rc Index. *Behav Ther* 1986;17(3):305-08. doi: Doi 10.1016/S0005-7894(86)80060-0
25. Guyatt GH, Osoba D, Wu AW, et al. Methods to explain the clinical significance of health status measures. *Mayo Clinic proceedings* 2002;77(4):371-83. doi: 10.1016/S0025-6196(11)61793-X
26. Jacobson NS, Roberts LJ, Berns SB, et al. Methods for defining and determining the clinical significance of treatment effects: description, application, and alternatives. *Journal of consulting and clinical psychology* 1999;67(3):300-7.
27. Jacobson NS, Truax P. Clinical significance: a statistical approach to defining meaningful change in psychotherapy research. *Journal of consulting and clinical psychology* 1991;59(1):12-9.
28. Kvien TK, Heiberg T, Hagen KB. Minimal clinically important improvement/difference (MCII/MCID) and patient acceptable symptom state (PASS): what do these concepts mean? *Annals of the rheumatic diseases* 2007;66 Suppl 3:iii40-1. doi: 10.1136/ard.2007.079798
29. Maksymowych WP, Richardson R, Mallon C, et al. Evaluation and validation of the patient acceptable symptom state (PASS) in patients with ankylosing spondylitis. *Arthritis and rheumatism* 2007;57(1):133-9. doi: 10.1002/art.22469
30. Norman GR, Sloan JA, Wyrwich KW. Interpretation of changes in health-related quality of life: the remarkable universality of half a standard deviation. *Medical care* 2003;41(5):582-92. doi: 10.1097/01.MLR.0000062554.74615.4C
31. Norman GR, Sridhar FG, Guyatt GH, et al. Relation of distribution- and anchor-based approaches in interpretation of changes in health-related quality of life. *Medical care* 2001;39(10):1039-47.
32. Pham T, van der Heijde D, Altman RD, et al. OMERACT-OARSI initiative: Osteoarthritis Research Society International set of responder criteria for osteoarthritis clinical trials revisited. *Osteoarthritis and cartilage / OARS, Osteoarthritis Research Society* 2004;12(5):389-99. doi: 10.1016/j.joca.2004.02.001
33. Revicki D, Hays RD, Cella D, et al. Recommended methods for determining responsiveness and minimally important differences for patient-reported outcomes. *Journal of clinical epidemiology* 2008;61(2):102-9. doi: 10.1016/j.jclinepi.2007.03.012
34. Tubach F, Ravaud P, Baron G, et al. Evaluation of clinically relevant changes in patient reported outcomes in knee and hip osteoarthritis: the minimal clinically important improvement. *Annals of the rheumatic diseases* 2005;64(1):29-33. doi: 10.1136/ard.2004.022905

35. Tubach F, Ravaud P, Baron G, et al. Evaluation of clinically relevant states in patient reported outcomes in knee and hip osteoarthritis: the patient acceptable symptom state. *Annals of the rheumatic diseases* 2005;64(1):34-7. doi: 10.1136/ard.2004.023028
36. Judge A, Cooper C, Williams S, et al. Patient-reported outcomes one year after primary hip replacement in a European Collaborative Cohort. *Arthritis care & research* 2010;62(4):480-8. doi: 10.1002/acr.20038
37. Goldstein H. Multilevel Statistical Models2002.
38. Browne WJ, Draper D. Implementation and performance issues in the Bayesian and likelihood fitting of multilevel models. *Computation Stat* 2000;15(3):391-420. doi: DOI 10.1007/s001800000041
39. King MT. A point of minimal important difference (MID): a critique of terminology and methods. *Expert Rev Pharmacoecon Outcomes Res* 2011;11(2):171-84. doi: 10.1586/erp.11.9
40. Schuck P, Zwingmann C. The 'smallest real difference' as a measure of sensitivity to change: a critical analysis. *Int J Rehabil Res* 2003;26(2):85-91. doi: 10.1097/01.mrr.0000070759.63544.65
41. Wylde V, Gooberman-Hill R, Horwood J, et al. The effect of local anaesthetic wound infiltration on chronic pain after lower limb joint replacement: a protocol for a double-blind randomised controlled trial. *BMC musculoskeletal disorders* 2011;12:53. doi: 10.1186/1471-2474-12-53
42. Altman DG, Gore SM, Gardner MJ, et al. Statistical guidelines for contributors to medical journals. *British medical journal* 1983;286(6376):1489-93.
43. Sterne JA, Davey Smith G. Sifting the evidence-what's wrong with significance tests? *Bmj* 2001;322(7280):226-31.
44. McConnell S, Kolopack P, Davis AM. The Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC): A review of its utility and measurement properties. *Arthrit Rheum-Arthr* 2001;45(5):453-61. doi: Doi 10.1002/1529-0131(200110)45:5<453::Aid-Art365>3.0.Co;2-W
45. Twisk J, Rijmen F. Longitudinal tobit regression: A new approach to analyze outcome variables with floor or ceiling effects. *Journal of clinical epidemiology* 2009;62(9):953-58. doi: DOI 10.1016/j.jclinepi.2008.10.003
46. Ram N, Grimm KJ. Growth mixture modeling: A method for identifying differences in longitudinal change among unobserved groups. *Int J Behav Dev* 2009;33(6):565-76. doi: Doi 10.1177/0165025409343765
47. Jones G, Lyons P. Approximate graphical methods for inverse regression. *Journal of Data Science* 20009;7:61-72.
48. Snijders TAB, Bosker RJ. Multilevel Analysis: An Introduction to Basic and Advanced Multilevel Modeling, second edition. London: Sage Publishers 2012.
49. Fieuws S, Verbeke G. Pairwise fitting of mixed models for the joint modeling of multivariate longitudinal profiles. *Biometrics* 2006;62(2):424-31. doi: 10.1111/j.1541-0420.2006.00507.x
50. Fieuws S, Verbeke G. Joint modelling of multivariate longitudinal profiles: pitfalls of the random-effects approach. *Statistics in medicine* 2004;23(20):3093-104. doi: 10.1002/sim.1885
51. Verbeke G, Molenberghs G. Linear mixed models for longitudinal data. USA: Springer 2000.
52. Rasbash J, Steele F, Browne WJ, et al. A user's guide to MLwIN. UK2009.
53. Copas JB. Regression, Prediction and Shrinkage. *J R Stat Soc B* 1983;45(3):311-54.
54. Fitzmaurice GM, Laird NM, Ware JH. Applied Longitudinal Analysis. USA: Wiley 2004.
55. Kenward MG, Roger JH. Small sample inference for fixed effects from restricted maximum likelihood. *Biometrics* 1997;53(3):983-97.
56. Pan HQ, Goldstein H. Multi-level repeated measures growth modelling using extended spline functions. *Statistics in medicine* 1998;17(23):2755-70. doi: Doi 10.1002/(Sici)1097-0258(19981215)17:23<2755::Aid-Sim41>3.0.Co;2-E

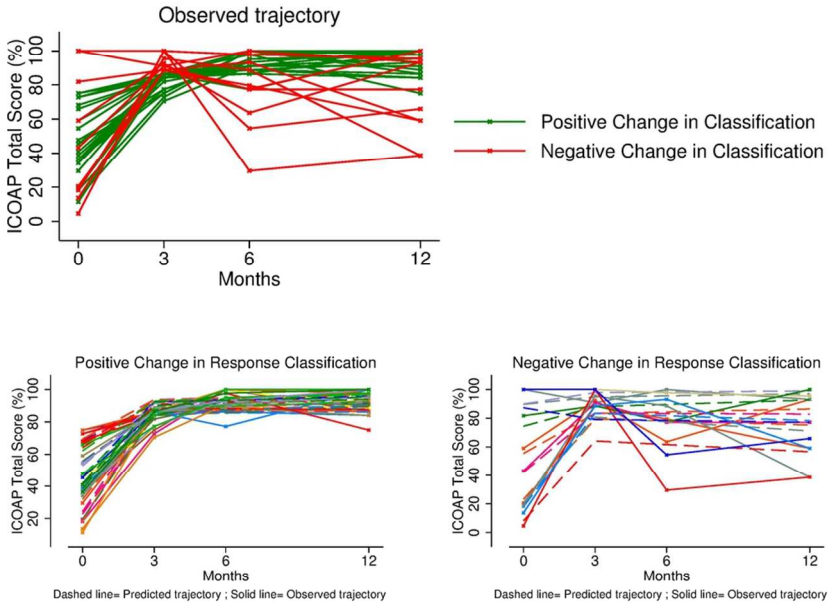
57. Rabe-Hesketh S, Skrondal A. Multilevel and latent variable modeling with composite links and exploded likelihoods. *Psychometrika* 2007;72(2):123-40. doi: DOI 10.1007/s11336-006-1453-8
58. Nagin DS, Odgers CL. Group-Based Trajectory Modeling in Clinical Research. *Annu Rev Clin Psycho* 2010;6:109-38. doi: DOI 10.1146/annurev.clinpsy.121208.131413
59. Lenguerrand E, Wylde V, Gooberman-Hill R, et al. Trajectories of Pain and Function after Primary Hip and Knee Arthroplasty: The ADAPT Cohort Study. *PLoS One* 2016;11(2):e0149306. doi: 10.1371/journal.pone.0149306
60. Sayers A, Wylde V, Lenguerrand E, et al. Rest Pain and Movement-Evoked Pain as Unique Constructs in Hip and Knee Replacements. *Arthritis care & research* 2016;68(2):237-45. doi: 10.1002/acr.22656
61. Bellamy N, Carette S, Ford PM, et al. Osteoarthritis antirheumatic drug trials. III. Setting the delta for clinical trials--results of a consensus development (Delphi) exercise. *The Journal of rheumatology* 1992;19(3):451-7.



296x419mm (300 x 300 DPI)



101x73mm (300 x 300 DPI)



101x73mm (300 x 300 DPI)

```
*******************************************************************************
*  A unified multi-level model approach to assessing patient responsiveness
*  including; return to normal, minimally important differences, and minimally
*  clinical important differences for patient reported outcome measures.
*******************************************************************************
*
*  Sayers A*, Wylde V, Lenguerrand E, Gooberman-Hill R, Dawson J, Beard D,
*  Price A, Blom AW
*
*  1.   Musculoskeletal Research Unit, School of Clinical Sciences,
*       University of Bristol, Southmead Hospital, Westbury On Trym,
*              Bristol, BS10 5NB.
*  2.   Nuffield Department of Population Health, University of Oxford,
*              Old Road Campus, Headington, Oxford OX3 7LF, UK
*  3.   Biomedical Research Unit, Nuffield Department of Orthopaedics,
*              Rheumatology and Musculoskeletal Science, Nuffield Orthopaedic Centre,
*              Windmill Road, Oxford, OX2 9JA
*
*      Address for Correspondence
*   Adrian Sayers, Musculoskeletal Research Unit, School of Clinical Sciences,
*   University of Bristol, Learning and Research Building (Level 1),
*   Southmead Hospital, Westbury on Trym, Bristol, BS10 5NB
*
*
*   E-mail: adrian.sayers@bristol.ac.uk
*   Tel: 44 (0)117 4147880; Fax + 44(0)117 414 7924
*******************************************************************************
* Abstract
* Stata code to illustrate calculation of patient reponsiveness using existing
* and multi-level model methods.
* Do file should be run comlpletely inorder to simulate data from a linear model
* and perform calculations.
* File requires MLWin and copy of runmlwin downloaded for Stata.

*******************************************************************************
* 1. Simulate a dataset
*******************************************************************************
{
* Design matrix in OO Format
set seed 111
clear
set obs 100
gen id= _n

* Set Parameters values
       * Set Fixed Effect Parameters
       local b0 = 49.19
              local b1 = 44.35 / 3
                     local b2 = 39.12
```

```
                        local b3 = 47.66 / 3
* Set Random Effect Standard Deviations & Correlation Matrix
local u0 = 25.3
        local u1 = 23.4 / 3
                local u2 = 18.5
                        local u3 = 19.1 / 3
                                matrix u = (`u0',`u1',`u2',`u3')'
                                        matrix u_corr = (1   ,0.3 ,0.1 ,0.1 \  ///
                                                         0.3 ,1   ,0.1 ,0.1 \  ///
                                                         0.1 ,0.1 ,1   ,0.3 \  ///
                                                         0.1 ,0.1 ,0.3 ,1   )
* Draw Random Parameters
        drawnorm u0 u1 u2 u3 , sds(u) corr(u_corr)


* Create 4 measurement occassions
expand 4
by id , sort : gen t = _n-1

* Prepare for a reshape into double long
gen _1= 1
        gen _2= 1
                reshape long _ , i(id t) j(resp)
                        drop _

* Set error Standard Deviations & Correlation Matrix
local e1= 5
        local e2= 5
                matrix e = (`e1', `e2')'
                        matrix e_corr = (1   ,0.1 \  ///
                                         0.1 ,1   )  //

                                drawnorm e1 e2 , sds(e) corr(e_corr)


* Create response indicators for OO
gen w1 = 1 if resp==1
        replace w1 = 0 if resp==2
                gen w2 = 0 if resp==1
                        replace w2 = 1 if resp==2

* Generate a satisfaction indicator, uncorrelated with effects just for illustration
gen x = cond(uniform()>=0.3,1,0) if resp==1 & t==1
        by id : egen _x = min(x)
                *Create dummy variables
                        gen x1 = 1 if _x==1
                                replace x1 = 0 if _x==0
                                        gen x2 = 0 if _x==1
                                                replace x2 = 1 if _x==0
```

```
                                                drop x _x


* Predict response
gen y = (`b0' + u0)* w1 + (`b1' + u1)* w1 * t + e1* w1 + ///
               (`b2' + u2)* w2 + (`b3' + u3)* w2 * t + e2* w2 //

tempfile simdata
       save `simdata' , replace

}
*******************************************************************************
* 2.1 Existing Methods (n.b. only for first response)
*******************************************************************************
use  `simdata' , clear
       * Working with the first and last measurment occassion
              keep if  t ==0 | t==3
                     sort id resp t
                            by id resp : gen d_y = y[_n] - y[_n-1]
*********************
* 2.1.1 Existing RTN
*********************
{
       sum y if t==0 & resp==1
              local rtn = r(mean) + 2*r(sd)
                     by id resp: gen ex_rtn =cond(y>=`rtn',1 ,0) if _n==2 & resp==1
                            by id resp: gen ex_rci = cond((d_y / sqrt(2*(`r(sd)' * sqrt(1-0.9))^2))>=1.96,1,0) if _n==2 & resp==1
                                   by id resp: gen ex_rtn_rci = cond(ex_rtn==1 & ex_rci==1 ,1,0) if _n==2 & resp==1

                                   tab ex_rtn if resp==1         // Number of individuals returning to normal
                                   tab ex_rci if resp==1         // Number of individuals significant change
                                   tab ex_rtn_rci if resp==1     // Number of individuals significant change & returning to normal
                                   }
*********************
* 2.1.2 Existing MID
*********************
{
sum y if t==0 & resp==1
       local mid = r(sd)*0.5
              by id resp : gen ex_mid =cond(d_y>=`mid',1,0)  if _n==2 & resp==1

                     tab ex_mid if resp==1         // Number of individuals with minimally important difference
}
*********************
* 2.1.3 Existing MCID
* n.b using the 25th centile is pain is reverse coded.
*********************
{
centile d_y if resp==1 & x1==1 , c(25)
```

```
        local mcid = r(c_1)
                by id resp: gen ex_mcid = cond(d_y>=`mcid',1,0) if _n==2 & resp==1

                        tab ex_mcid if resp==1        // Number of individuals meeting the MCID criteria
}

*******************************
* 2.1.4 Existing (OO) OMERACT-OARSI
*******************************
{
* 50% relative, 20% absolute single
* 20% relative, 10% absolute both

* Calculate Relative Change
        by id resp: gen d_rely= (d_y/y[_n-1])*100
                * Mark Single Changes
                        by id resp: gen ex_oo_single =1 if (d_y>=20 & d_y<.) | (d_rely>=50 & d_rely<.) & _n==2
                                * Mark Double Changes
                                        by id resp: gen ex_oo_double =1 if (d_y>=10 & d_y<.) | (d_rely>=20 & d_rely<.) & _n==2
                                                * Sum double changes
                                                        by id  : egen ex_oo_double_sum = total(ex_oo_double) if  d_y!=.

* Mark OO criteria
        by id : gen _ex_oo = cond(ex_oo_single==1 | ex_oo_double_sum==2 , 1,0) if d_y!=.
                by id : egen ex_oo = max(_ex_oo) if d_y!=.

                tab ex_oo if resp==1   // Number of individuals meeting the oo criteria
}
*******************************************************************************
* 2.2 Multi-level Methods
*******************************************************************************
// Set the global macro to identify the location and version of mlwin
global MLwiN_path "C:\Program Files (x86)\MLwiN v2.36\i386\MLwiN.exe"
        use  `simdata' , clear
                keep if resp==1
* Create a constant
gen cons=1

******************
* 2.2.1 MLM RTN / MID Model
******************
{
*                       0-----------------1
*                       1,2,3,4,5,6,7,8,9,0,1,2,3,4,5,6,7,8,9,0,
matrix a = (1,1,1)

runmlwin y cons t if resp==1 ,                                                          /// Fixed effect
        level1(t: cons, residuals(_e, )  )                                  /// Level 1 variance
                level2(id: cons t, elements(a) residuals(_u, ) )     /// Level 2 varaince
```

```
                    maxiterations(10)  corr sd nopause                          //      Modelling options

* Predict Individual effects
gen xb_fe =  _b[cons] + _b[t]*t
       gen xb_re =  _u0 + _u1*t
              gen xb = xb_fe + xb_re

* Predict to asses responsiveness at (3month)
gen xb_t =  (_b[cons]+_u0) + (_b[t]+_u1)*3

* RTN threshold
local mlm_rtn = _b[FP1:cons] + 2*(_b[RP2:var(cons)]^0.5)

* Mark RTN
gen mlm_rtn = cond(xb_t>=`mlm_rtn',1,0)

* Calculate RCI
       gen xb_d = _b[FP1:t] + _u1
              gen se_d = (_se[FP1:t]^2 +_u1se^2)^0.5
                     gen z_d = xb_d / se_d

* Mark RCI
gen mlm_rci = cond(z_d>=1.96,1,0)

* Mark RTN RCI composite
gen mlm_rtn_rci = cond(mlm_rtn==1 & mlm_rci==1, 1, 0)
       egen pickone = tag(id)

              tab mlm_rtn_rci if pickone==1 // Number of individuals meeting the MLM RTN RCI  criteria
}
**********************
* 2.2.2 MLM MID
**********************
{
* MID Threshold @ 3 months
local mlm_mid = 0.5*(_b[RP2:var(cons)]^0.5)
       gen mlm_mid = cond( (_b[t]+_u1)*3>= `mlm_mid' ,1 ,0 )
              tab mlm_mid if pickone==1 // Number of individuals meeting the MLM MID criteria

* Drop previous residual and predictions
drop  _u0 _u1 _u0se _u1se _e0 _e0se  xb_fe xb_re xb xb_t xb_d se_d z_d
}
********************
* 2.2.3  MLM MCID
********************
{
* Stratify intercept and slope by satisfaction
gen consx1= cons*x1
       gen consx2 = cons*x2
```

```
                gen tx1 = t*x1
                        gen tx2 = t*x2

* Specify RE variance matrix
*                       0-----------------1-------------------2
*                       1,2,3,4,5,6,7,8,9,0,1,2,3,4,5,6,7,8,9,0,1
matrix u = (1,1,1,0,0,1,0,0,1,1)

* Specify RE variance matrix
*                       0-----------------1-------------------2
*                       1,2,3,4,5,6,7,8,9,0,1,2,3,4,5,6,7,8,9,0,1
matrix e = (1,0,1)

runmlwin y consx1 tx1 consx2 tx2 if resp==1 ,                                                                   /// Fixed effect
        level1(t: consx1 consx2, elements(e)  residuals(_e, norecode ))                         /// Level 1 variance
                level2(id: consx1 tx1 consx2 tx2 ,elements(u)  residuals(_u, norecode ))   /// Level 2 varaince
                        maxiterations(10)  corr sd nopause                                                              //      Modelling
options

* Estimate the Change  for all individuals
gen xb_slope = (_b[tx1]+_u1)*x1 + (_b[tx2]+_u3)*tx2

* Find the 75th (inverse coding 25th) centile of those satisfied
centile xb_slope if tx1==3 , c(25)
        local mlm_mcid = r(c_1)

*tag observations which have improvements greater than mcid
        gen mlm_mcid = cond(xb_slope>=`mlm_mcid',1,0) if t==3
                tab mlm_mcid if t==3 // Number of individuals meeting the MCID  criteria
        }
*********************
* 2.2.4  MLM (OO) OMERACT-OARSI
*********************
{
* 50% relative, 20 absolute single assuming a 0-100 score
* 20% relative, 10 absolute both assuming a 0-100 score
use  `simdata' , clear
        sort id t resp


* Create response indicators
gen cons =1
        gen consw1 = cons*w1
                gen consw2 = cons*w2
                        gen tw1 = t*w1
                                gen tw2 = t*w2

runmlwin y  consw1 tw1 consw2  tw2 ,                                                                    /// Fixed Effect
        level1(resp:)                                                                                   /// Level 1 variance
```

```
        level2(t: consw1 consw2,  residuals(_e, norecode ))                              /// Level 2 variance
                level3(id: consw1 tw1 consw2 tw2 , residuals(_u, norecode ))        /// Level 3 varaince
                        maxiterations(10)  corr sd nopause                                                      //      Modelling options

* Calculate predicted changes
gen mlm_d = (_b[tw1] + _u1 )*tw1  + (_b[tw2] + _u3 )*tw2
        gen mlm_bl = (_b[consw1] + _u0)*consw1 + (_b[consw2] + _u2)*consw2
                gen mlm_relyd=  (mlm_d /mlm_bl)*100

* Mark out responders
                        by id resp ,sort: gen mlm_oo_single =1 if (( mlm_d>=20 & mlm_d<.) | (mlm_relyd>=50 & mlm_relyd<.)) & t==3
                                * Mark Double Changes
                                        by id resp ,sort: gen mlm_oo_double =1 if ((mlm_d>=10 & mlm_d<.) | (mlm_relyd>=20 & mlm_relyd<.)) & t==3
                                                * Sum double changes
                                                        by id ,sort  : egen mlm_oo_double_sum = total(mlm_oo_double) if t==3

* Mark OO criteria
by id : gen _mlm_oo = cond(mlm_oo_single==1 | mlm_oo_double_sum==2 , 1,0) if t==3
        by id : egen mlm_oo = max(_mlm_oo) if t==3

                tab mlm_oo if resp==1  // Number of individuals meeting the MLM OO criteria
}
```

BMJ Open

A unified multi-level model approach to assessing patient responsiveness including; return to normal, minimally important differences, and minimal clinical important improvement for patient reported outcome measures.

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2016-014041.R2
Article Type:	Research
Date Submitted by the Author:	10-May-2017
Complete List of Authors:	Sayers, Adrian; University of Bristol, Muscloskeletal Research Unit Wylde, Vikki; University of Bristol, School of Clinical Sciences Lenguerrand, Erik; University of Bristol School of Clinical Science, School of Clinical Sciences, Musculoskeletal Research Unit Gooberman-Hill, Rachael; University of Bristol, School of Clinical Sciences Dawson, Jill; University of Oxford, Department of Public Health Beard, David; University of Oxford, Nuffield Dept of Orthopaedics, Rheumatology and Musculoskeletal Sciences Price, Andrew; University of Oxford, Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences Blom, Ashley; University of Bristol, School of Clinical Sciences
Primary Subject Heading:	Research methods
Secondary Subject Heading:	Rheumatology, Epidemiology, Patient-centred medicine
Keywords:	Patient Responsiveness, Multi-level Modelling, Return To Normal, Minimal Important Difference, Patient-reported outcomes, Minimial clinical important improvement

A unified multi-level model approach to assessing patient responsiveness including; return to normal, minimally important differences, and minimal clinical important improvement for patient-reported outcome measures.

Sayers A[1,2], Wylde V[1], Lenguerrand E[1], Gooberman-Hill R[1], Dawson J[3], Beard D[4], Price A[4], Blom AW[1]

Address for Correspondence

Adrian Sayers, Musculoskeletal Research Unit, School of Clinical Sciences, University of Bristol, Learning and Research Building (Level 1), Southmead Hospital, Westbury on Trym, Bristol, BS10 5NB

E-mail: adrian.sayers@bristol.ac.uk

Tel: 44 (0)117 4147880; Fax + 44(0)117 414 7924

1. Musculoskeletal Research Unit, School of Clinical Sciences, University of Bristol, Southmead Hospital, Westbury On Trym, Bristol, BS10 5NB (AS, VW, EL, RGH, AWB).
2. School of Social and Community Medicine, University of Bristol, 39 Whatley Road, Bristol, BS8 2PS.
3. Nuffield Department of Population Health, University of Oxford, Old Road Campus, Headington, Oxford OX3 7LF, UK (DB, AP).
4. Biomedical Research Unit, Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Science, Nuffield Orthopaedic Centre, Windmill Road, Oxford, OX2 9JA (JD).

Word Count 4010

Keywords: Patient Responsiveness, Multi-level Modelling, Return To Normal, Minimal Important Difference, Minimal Clinically Important Difference, Patient-reported outcomes, Clinical significance Anchor-based methods; Distribution-based methods

Abstract (271 Words)

Objective

This article reviews and compares four commonly used approaches to assess patient responsiveness to a treatment or therapy [Return To Normal (RTN), Minimal Important Difference (MID), Minimal Clinically Important Improvement (MCII), OMERACT-OARSI (OO)], and demonstrates how each of the methods can be formulated in a multi-level modelling (MLM) framework.

Design

Cohort Study

Setting

A cohort of patients undergoing total hip and knee replacement were recruited from a single UK NHS hospital.

Population

400 Patients from The Arthroplasty Pain Experience (APEX) cohort study undergoing total hip (n=210) and knee (n=190) replacement who completed the Intermittent and Constant Osteoarthritis Pain (ICOAP) questionnaire prior to surgery and then at 3, 6 and 12 months after surgery.

Primary Outcomes

The primary outcome was defined as a response to treatment following total hip or knee replacement. We compared baseline scores, change scores, and proportion of individuals defined as "responders" using traditional and MLM approaches to patient responsiveness.

Results

Using existing approaches, baseline and change scores are underestimated, and the variance of baseline and change scores overestimated in comparison to MLM approaches. MLM increases the proportion of individuals defined as responding in RTN, MID, and OO criteria compared to existing approaches. Using MLM with the MCII criteria reduces the number of individuals identified as responders.

Conclusion

MLM improves the estimation of the standard deviation of baseline and change scores by explicitly incorporating measurement error into the model, and avoiding regression to the mean when making individual predictions. Using refined definitions of responsiveness may lead to a reduction in misclassification when attempting to predict who does and does not respond to an intervention, and clarifies the similarities between existing methods.

Article Summary

Strengths and limitations of this study

- Four different approaches to patient responsiveness can be unified into a multi-level model.
- A multi-level model framework of patient responsiveness highlights the similarities and differences between existing methods.
- Multi-level models provide a simple framework which incorporates measurement error and non-linear change in trajectories of patient recovery.
- Multi-level models are technically more demanding than existing formulations of patient responsiveness, and convergence is not guaranteed.
- Multi-level models does not improve the arbitrary placement of the thresholds that define responsiveness in comparison to existing methods

INTRODUCTION

Joint replacement is an increasingly common elective procedure worldwide [1-3] and improving patient-reported outcomes after joint replacement is a key research priority due to the high prevalence of poor outcomes after joint arthroplasty.[4] Poor outcomes include continuing pain, functional limitations,[5] and increased healthcare utilisation.[6] However, there is some debate on how the efficacy of interventions can be judged due to the variety of different outcomes used in orthopaedic research.[7-18] Traditionally, objective primary outcomes such as prosthetic survivorship and mortality rates were used.[19] However, more recently there has been a shift in focus which ensures that patients' perspective is central to the assessment of intervention success.[20] Many studies now use patient-reported outcome measures (PROMs) as endpoints, and these tools can assess a variety of health outcomes, including pain,[7 21] physical functioning,[7] mental well-being[22] and health-related quality of life.[23]

Although PROMs are widely used,[4] there is still debate in how the results should be interpreted and how to define a clinically meaningful change.[24-35] From a measurement perspective, the ability to estimate if a change has occurred depends on the application of an appropriate statistical model. From a clinical perspective, some authors suggest that the average statistical change is insufficient to "tell you anything about an individual's chances of improving".[36] Therefore, the utility of simple statistical analyses are limited when attempting to help patients weigh up the risks and benefits of undergoing surgery.

In order to supplement simple statistical analysis, many researchers attempt to dichotomise the population into those who have or have not responded to an intervention, creating a two-stage process of defining an outcome. There are a number of different methods (definitions) that can be used to dichotomise the population, and these secondary analyses are collectively referred to as responsiveness analyses.[36] Four substantively different methods of estimating the proportion of individuals who respond to an intervention have been previously identified in orthopaedic

research:[36] 1) Return to Normal (RTN), 2) Distribution-based Minimally Important Difference (MID), 3) Anchor-based Minimal Clinically Important Difference (MCII), and 4) the OMERACT-OARSI (OO) responder criteria. The first three approaches are generic and used in many fields of health research, whereas the fourth approach is specific to orthopaedic research, but in principle could be used in many fields of health research.

Each of these approaches is often thought to be methodologically distinct. However, all of the methods can be shown to be special cases of a multi-level model (MLM). MLM have been used in a wide variety of contexts ranging from growth modelling to modelling educational data. One of the principal reasons to use MLM is to take advantage of the direct estimation of different variance components[37] and provide efficient and unbiased estimates of fixed and random effects.[38]

Despite a number of extensive reviews of patient responsiveness,[31 33 39 40] we will describe these four approaches to calculating responsiveness and highlight the substantively different decisions each method makes. We will then describe how each approach can be translated into a MLM framework, emphasising the benefits of the translation, and contrast the approaches using an example from the APEX cohort study.[41]

METHODS

We outline the four existing approaches to patient responsiveness previously used in orthopaedic research [36], and describe their potential limitations, and how they can be formulated in a MLM framework.

Review of existing approaches to responsiveness

Return to normal (RTN)[26] suggests that an individual has returned to 'normal' if their score on a post-intervention outcome is greater than two standard deviations (SD) from the mean baseline response.

The use of two standard deviations appears to be justified on theoretical grounds, however it is quite arbitrary. Assuming scores are normally distributed and measured without error, two SD's corresponds to a 95.5% prediction interval for the mean, which is similar to the equally arbitrary and much-criticised significance threshold p=0.05 (Type I error=0.05) criterion used throughout medical research[42 43]. However, there is no reason why a 1.6 or a 2.6 SD cut-offs should not be used in preference, which corresponds to 90% and 99% prediction intervals.

The method also assumes the observed change is unlikely to be due to chance alone and does not account for any uncertainty. In order to alleviate this problem the use of the Relative Change Index (RCI) was proposed to be used in conjunction with the RTN classification.[24 27] The RCI constructs a test of the individual's score at follow-up compared to their baseline, where the standard error of the difference is estimated indirectly using the SD of the baseline score and an assumed reliability coefficient from empirical research or a range of reliability values in the spirit of a sensitivity analysis.

A commonly described distribution-based Minimally Important Difference (MID) method classifies individuals as responders if their observed change is greater than a fixed proportion of the SD of the pre-surgery score.[30] There has been much debate about the exact size, or proportion, of the SD change score to use, however 0.5 SD's has been reported widely and suggested to be a difference

that is minimally perceptible to patients.[30] Any individual with a change score greater than 0.5 SD of the baseline score is defined as responding to the treatment. Similar to the RTN criteria, the decision to use 0.5 is arbitrary and there is no reason why more or less stringent criteria of 0.25, 1 or 2 SD's could not be used. Additionally, there is no reason why a test such as the RCI should not be conducted to check that change is beyond the bounds of measurement error.

Anchor-based Minimal Clinically Important Improvement (MCII) is similar to the MID approach, in that it defines an individual as a responder based on their individual change score. However, the cut-point is determined in individuals who report themselves as having an outcome which is either good/satisfactory or perceived as improved from baseline using an external anchoring question. The authors proposed using a cut point at the 75th centile of the change score, in those who are satisfied.[34] Therefore any individuals, whether they are satisfied or not, who has a change score greater than the 75th centile are defined as responders. A closely related anchor-based metric is the Patient Acceptable Symptom State (PASS),[35] the construction is similar to that of the MCII with the exception that it is based on the final score of patients opposed to change. Conceptually the PASS is more closely related to the RTN definition of responsiveness, and much of the criticism levied against MCII and RTN can therefore be applied to the PASS.

The OMERACT-OARSI (OO) criteria[32] recognises that a response to an intervention may occur in one or more different measured outcomes, i.e. a multivariate response mechanism. In keeping with much of the orthopaedic literature they assume the proposed score has been rescaled between 0 and 100 [32], and that a responder is defined as any individual with 1. a >=50% relative change or a >=20 point absolute change on one or more responses scales, or 2. a >=20% relative change or >=10 point absolute change in two or more response scales. Relative change is defined as the ratio of the change to the individual baseline score multiplied by 100. Unlike the RTN, MID, or MCII it is very clear that the thresholds for relative and absolute changes are based on a panel of expert opinions and are fixed.

Despite the variety of existing approaches used to identifying responders, there are a number of problems common to all methods. Common assumptions include: 1) Each observed outcome is measured without error and reflects the true underlying patient's response, test-retest reliability studies indicate that this is not a realistic assumption .[44] 2) Regression to the mean does not occur and therefore the variance of the change score will not be overestimated. 3) Floor and ceiling effects do not bias estimates of the variance of the change score.[45]

Furthermore, in RTN, specific combinations of means and variances may result in a threshold beyond the range of the measurement tool, therefore no individuals would be defined as responding to a therapy. The MCII approach assumes the additional anchoring variable is measured without error and the response trajectory is distinct from those who are unsatisfied.[46] The method also assumes a two parameter logistic function is an appropriate model for the cumulative proportional rank of patients and change in outcome, and that there is no uncertainty in the calculation of the threshold .[47] Finally, the OO approach considers a response in two or more outcomes. However, it does not explicitly describe how the correlation between the two outcomes is accounted for and fails to recognise that if not modelled appropriately may introduce bias.[48-50]

The four methods identified have a number of other limitations,[25] but they are difficult to compare methods when presented as distinct approaches.

Embedding them in a unified statistical framework makes their underlying assumptions explicit, whilst highlighting their similarities and differences. In addition, it provides a framework to incorporate non-linear change, measurement error, and variability in the timing of measurement occasions, all of which are to be expected in real word data collections and are critical when attempting to asses a patients change at a specified point in time.

Multi-level modelling approach to responsiveness

We now present a general multi-level model for patient responsiveness and show how the four approaches described above can be specified as special cases.

Under the assumption of linear change, the measured response (y) at the i^{th} occasion for the j^{th} individual is modelled as a linear function of time.

Equation 1

$$y_{ij} = \beta_0 + u_{0j} + (\beta_1 + u_{1j})t_{ij} + \varepsilon_{ij}$$

$$\begin{bmatrix} u_{0j} \\ u_{1j} \end{bmatrix} \sim N(0, \Omega_u), \qquad \Omega_u = \begin{bmatrix} \sigma^2_{u0} & \\ \sigma_{u01} & \sigma^2_{u1} \end{bmatrix}$$

$$[\varepsilon_{ij}] \sim N(0, \sigma^2_\varepsilon)$$

where t_{ij} is the time at which measurement i was taken on individual j, coded as zero at baseline. β_0 is the baseline population average response, and u_{0j} represents the j^{th} individual difference from the baseline response. The sum of $\beta_0 + u_{0j}$ is the estimated individual baseline response. β_1 represents the population average change per unit increase in time , and u_{1j} represents the j^{th} individual difference from the population average change per unit increase in time. The sum of $\beta_1 + u_{1j}$ is the estimated individual average change per unit increase in time. Measurement error in the linear trajectory is represented by ε_{ij}.

The variance in individual deviations from the population average response at baseline and average rate of change are σ^2_{u0} and σ^2_{u1} respectively. Furthermore, the correlation between baseline measurements and rate of change can be assumed to be independent or correlated by constraining σ_{u01} to be zero or allowing it to be freely estimated. The variances of the shrunken residuals $\hat{u}_{0j}$ and $\hat{u}_{1j}$, also known as empirical bayes estimates, are typically less than the estimated population variances $\hat{\sigma}^2_{u0}$ and $\hat{\sigma}^2_{u1}$ as they shrink towards the population averages of β_0 and β_1 . The extent of the shrinkage depends on the number of measurement occasions and the within individual

variability, with greater shrinkage as the number of measurement occasions decrease and as the within individual variance increases. A more detailed discussion of MLM can be found in most advanced statistics textbooks.[48 51 52]

We now describe how the four traditional approaches to measuring patient responsiveness can be unified into a MLM framework. General benefits of the MLM over existing approaches include: 1) with more than three measurement occasions a MLM directly allows for measurement error, ε_{ij} ; 2) the use of shrunken residuals $\widehat{u_{0j}}$ and $\widehat{u_{1j}}$ allow for regression to the mean when predicting an individual's score [53]; 3) MLM can be extended to include multivariate response models which appropriately model the correlation between two or more outcomes; and 4) MLM allows for variability in the timing of measurement occasions. Fundamentally, the MLM approach recognises that observed patient responses are subject to error, and therefore the true patient's response following an intervention must be estimated.

MLM-Return To Normal. In order to apply the RTN criteria using a MLM approach we first estimate the baseline population SD in individuals considered to be abnormal using the model described in Equation 1. Assuming y_{ij} is normally distributed at baseline with a population mean β_0 and variance σ_{u0}^2 a $100 \cdot \left(1 - \frac{\alpha}{2}\right)$ prediction interval for the baseline measurement can be constructed i.e. $\left[\beta_0 - \sigma_{u0}\mathrm{z}_{\left(1-\frac{\alpha}{2}\right)}, \beta_0 + \sigma_{u0}\mathrm{z}_{\left(1-\frac{\alpha}{2}\right)}\right]$ where α is the type I error rate and z is the critical value from a standard normal distribution. Importantly y_{ij} is not assumed to be measured without error and therefore estimates of σ_{u0}^2 are less likely to be biased than using simple methods. However, it is important to note that the choice of α is entirely that of the researcher, and whilst α =0.05 (leading to $z = 1.96 \approx 2$) is common, more or less stringent criteria could be applied.

The second step is to estimate the score of the individual at time *j* following surgery and determine if it is within the baseline prediction interval. This prediction is simply calculated by substituting

estimates of β_0 , β_1 , u_{0j} and u_{1j} into Equation 1, to give the empirical best linear unbiased prediction (eBLUP) for the j^{th} individual at the i^{th} occasion.[54]

Finally, in order to determine whether or not the response of the individual following surgery is greater than one would attribute to chance alone, i.e. the null hypothesis that the j^{th} individual's slope is not equal to zero, a test statistic similar to RCI should be conducted,

$(\hat{\beta}_1 + \hat{u}_{1j})/SE(\hat{\beta}_1 + \hat{u}_{1j})$, where $SE(\hat{\beta}_1 + \hat{u}_{1j}) = \sqrt{VAR(\hat{\beta}_1) + VAR(\hat{u}_{1j})}$.

MLM-Minimally Important Difference. The threshold of minimally important difference can also be estimated using a MLM. Similar to RTN, a linear model of change is applied, as in Equation 1. Then the population SD of the baseline response is estimated by σ_{u0}. By comparing the estimated change for the j^{th} individual $(\hat{\beta}_1 + \hat{u}_{1j})t$ to the baseline standard deviation, i.e. $\sigma_{u0}/2$, the individual can be classed as a responder or not. The MID approach does not specifically state whether a test of whether an individual's change scores is less than the MID threshold should be conducted, but a test statistic is simply constructed as $\left((\hat{\beta}_1 + \hat{u}_{1j})t - \left(\frac{\hat{\sigma}_{u0}}{2}\right)\right) \Big/ (SE(\hat{\beta}_1 + \hat{u}_{1j})t)$.

MLM-Minimally Clinically Important Improvement. The MLM MCII requires a simple extension of the univariate model presented previously (Equation 1). The outcome of interest is stratified using an external criterion. The stratification is achieved by creating dummy variables for those who are un/satisfied with some aspect of their treatment i.e. x_{1i} takes the values 0 and 1 representing unsatisfied and satisfied individuals respectively, and $x_{2i} = 1 - x_{1i}$. These dummy variables are then included as additional explanatory variables, with no overall model intercept, and interacted with *t.*

Equation 2

$$y_{ij} = (\beta_0 + u_{0j})x_{1i} + (\beta_1 + u_{1j})t_{ij}x_{1i} + \varepsilon_{1ij}x_{1i}$$

$$+ (\beta_2 + u_{2j})x_{2i} + (\beta_3 + u_{3j})t_{ij}x_{2i} + \varepsilon_{2ij}x_{2i}$$

$$\begin{bmatrix} u_{0j} \\ u_{1j} \\ u_{2j} \\ u_{3j} \end{bmatrix} \sim N(0, \Omega_u): \qquad \Omega_u = \begin{bmatrix} \sigma^2_{u0} & & & \\ \sigma_{u01} & \sigma^2_{u1} & & \\ 0 & 0 & \sigma^2_{u2} & \\ 0 & 0 & \sigma_{u23} & \sigma^2_{u3} \end{bmatrix}$$

$$\begin{bmatrix} \varepsilon_{1ij} \\ \varepsilon_{2ij} \end{bmatrix} \sim N(0, \Omega_\varepsilon): \qquad \Omega_\varepsilon = \begin{bmatrix} \sigma^2_{\varepsilon 1} & \\ 0 & \sigma^2_{\varepsilon 2} \end{bmatrix}$$

Therefore β_0 and β_2 are the mean population outcome score at baseline for those who are satisfied and unsatisfied respectively, and β_1 and β_3 are the corresponding mean population changes per unit of time. Variances and covariances are similarly interpreted for those who are satisfied and unsatisfied respectively. However, that satisfaction on the external anchoring question is assumed to be known without error, and individual effects and errors for x_{1i} are uncorrelated with those for x_{2i} because the satisfied and unsatisfied categories are mutually exclusive. Whether or not it is desirable to fit a model to both satisfied and unsatisfied individuals simultaneously is debateable, as only those who are satisfied contribute to the definition of MCII. However, we present a simultaneous modelling approach to satisfied and unsatisfied individuals as it make the underlying modelling assumptions explicit. Furthermore, if the stratification on satisfaction status leads to a small samples alternative estimators and degree of freedom can be used in a MLM framework to account for this i.e. restricted maximum likelihood, restricted generalised least squares, or adjustments to the denominator degrees of freedom.[55]

Following the prediction of each individual's trajectory, including those unsatisfied with treatment, the second stage in the MCII method requires a threshold for determining responsiveness. Using a similar suggestion to Tubach et al.,[35] the 75th centile of those who are satisfied could be used to classify all individuals as responding or not. Similar to the MID there is no suggestion of whether a

test against the null value of the 75th centile should be constructed, but this is easily done within the MLM framework.

MLM-OMERACT-OARSI criteria. The OO criteria can be similarly extended into a multi-variate MLM framework by the inclusion of dummy variables and reshaping into a "double" long format with both responses stored in a single vector. Figure 1 illustrates the data structure for a bivariate model.

Dummy variables, also known as response indicators, are used to denote the response options: w_{1i} is coded 1 for the first measurement outcome (pain) and 0 for the second outcome (function), and $w_{2i} = 1 - w_{1i}$. The response indicators and their interactions with t are included as explanatory variables to obtain the following bivariate response model.

Equation 3

$$y_{ij} = (\beta_0 + u_{0j})w_{1i} + (\beta_1 + u_{1j})t_{ij}w_{1i} + \varepsilon_{1ij}w_{1i}$$

$$+ (\beta_2 + u_{2j})w_{2i} + (\beta_3 + u_{3j})t_{ij}w_{2i} + \varepsilon_{2ij}w_{2i}$$

$$\begin{bmatrix} u_{0j} \\ u_{1j} \\ u_{2j} \\ u_{3j} \end{bmatrix} \sim N(0, \Omega_u): \qquad \Omega_u = \begin{bmatrix} \sigma_{u0}^2 & & & \\ \sigma_{u01} & \sigma_{u1}^2 & & \\ \sigma_{u02} & \sigma_{u12} & \sigma_{u2}^2 & \\ \sigma_{u03} & \sigma_{u13} & \sigma_{u23} & \sigma_{u3}^2 \end{bmatrix}$$

$$\begin{bmatrix} \varepsilon_{1ij} \\ \varepsilon_{2ij} \end{bmatrix} \sim N(0, \Omega_\varepsilon): \qquad \Omega_\varepsilon = \begin{bmatrix} \sigma_{\varepsilon 1}^2 & \\ \sigma_{\varepsilon 12} & \sigma_{\varepsilon 2}^2 \end{bmatrix}$$

With a similar functional form to the univariate MLM, there are separate population and individual intercepts for the first and second outcome (β_0 , β_2 and u_{0j}, u_{2j} respectively), and separate population and individual slopes are estimated for the second outcome $(\beta_1$, β_3 and $u_{1j}, u_{3j})$. Using a MLM approach the outcomes are modelled jointly, which allows for non-zero covariances

between the intercepts and slopes of the two responses ($\sigma_{u02}, \sigma_{u12}, \sigma_{u03}, \sigma_{u13}$). The measurement errors for the two responses are not assumed to be independent, with their covariance directly estimated ($\sigma_{\varepsilon 12}$).

Finally, the threshold of response must be decided and individual trajectories estimated and classified. Similar to the other methods it is relatively simple to construct a test statistic for testing whether individual slopes are significantly different from the chosen threshold.

Limitations of the MLM approach. The MLM approach described by Equation 1, Equation 2 and 3 assumes that change in the outcome is linearly associated with time. The linearity assumption is imposed for simplicity. Non-linear changes are easily incorporated by including higher order polynomials or using linear or non-linear splines.[56]

The standard MLM approach also fails to directly address the issue of floor and ceiling effects. Mixed response multi-level Tobit models allow for such effects and provide some adjustment.[45 57] Furthermore, whilst the MLM described in Equation 2 allow for heterogeneity in known groups, they fail to allow for heterogeneity in trajectories when the groups are unknown. The use of group-based trajectory models or growth mixture models in these circumstances may reveal latent (unobserved) classes of individuals with distinct patterns of recovery.[58]

Example: The APEX cohort Study

Using a mixed cohort of patients undergoing THR and TKR, [41] we investigated the performance of the existing and MLM approaches using four definitions of responsiveness. A simulated dataset and code to fit each of these models are included in the supplementary material.

Patients in the APEX cohort completed the Intermittent and Constant Osteoarthritis Pain (ICOAP) questionnaire before and after surgery at approximately 0, 3, 6 and 12 months. The date at which the post-surgical questionnaire was completed is recorded in days post-surgery. As the name suggests, the ICOAP questionnaire attempts to measure intermittent and constant pain. [21] The developers of the tool suggest three ways of summarising the scale to generate an intermittent, constant and total pain scores (the sum of the intermittent and constant pain subscales). The tool is scored between 0 and 100 and a full description of the ICOAP scale is provided in the original validation paper.[21] Satisfaction of pain relief following surgery was recorded by asking patients to "Rate the relief of pain provided by (hip/knee) replacement?" using a single item 5 point scale (None, Poor, Fair, Good, Excellent). We categorised good and excellent as a satisfactory outcome following surgery.

Using the three methods of aggregation, we present estimates of pain at baseline and for change at approximately 3 months post-surgery using existing methods (summary statistics) and MLM estimates.

In order to facilitate comparisons between existing and MLM approaches we assume that all individuals are measured at exactly 0, 3, 6, and 12 months. Whilst the existing approaches only utilises the 0 and 3-month measurements the MLM approach uses a random intercept and random slopes across 4 measurements occasions, using two linear splines with a knot point at 3 months to estimate the response at 3 months. The inclusion of the second spline and the additional two measurement occasions allows adjustment for measurement error in the MLM approach. Table 1

and 2 presents results for patients undergoing THR and TKR respectively. The placement of the knot at 3 months was determined by visually inspecting the data, similar to the methods by Lenguerrand et al.[59] With more complex patterns of response an iterative model fitting approach is likely to be required to determine the optimal knot placement. Modelling assumptions were checked using ladder plots, and normal plots of residuals.

To describe how the responsiveness classification in patients changed at 3 months, we used an Exact McNemar test to compare the number of discordant classifications generated by existing and MLM approaches.

The APEX study was approved by Southampton and South West Hampshire Research Ethics Committee (09/H0504/94).

RESULTS

In all subdivisions of the ICOAP questionnaire, for THR/TKR patients, the estimates of the baseline mean and change scores are approximately equal to those from the MLM approaches. In addition, estimates of the SD of baseline and change score are overestimated using existing approaches in THR/TKR patients. The SD of baseline measurements of pain were approximately 3.3 and 3.75 points greater in existing methods compared to MLM methods in THR/TKR patients respectively, while the corresponding SD of change scores are approximately 6.3 and 7 points greater in existing methods, see table 1 and 2 respectively. An example of model diagnostics is included in Figure 2, which presents the observed ICOAP total scores at 0, 3, 6, and 12 months and the population average response in ICOAP across time. In addition, baseline, change residuals are also presented using quantile-quantile plots.

Table 1: Mean and standard deviation of baseline and change scores estimated using current and multi-level model approaches to responsiveness in a patient undergoing total hip replacement in the APEX cohort study. Betas represent the population average characteristic and sigma the estimated standard deviation. Baseline is assumed to be the day of surgery, and change is from 0 to 3 months.

			Current Approaches to Responsiveness				Multi-Level Model Approaches to Responsiveness			
		N	Baseline β_0 σ_{u0}	Change β_1 σ_{u1}	Absolute Threshold	P(Resp.)	Baseline β_0 σ_{u0}	Change β_1 σ_{u1}	Absolute Threshold	P(Resp.)
Return to Normal	Total Pain	210	43.71 (22.1)	45.76 (24.0)	87.9	70.5 (63.8, 76.6)	43.71 (20.1)	46.14 (19.7)	83.8	78.1 (71.9, 83.5)
MID		210			11.0	91.9 (87.4, 95.2)			10.0	97.6 (94.5, 99.2)
MCID (Satisfied)		185	44.37 (22.0)	48.43 (22.6)	32.6	71.9 (65.3, 77.9)	44.37 (20.3)	48.54 (19.2)	35.8	67.1 (74.5, 85.6)
MCID (UnSatisfied)		25	38.77 (22.4)	26.05 (25.4)			38.77 (17.0)	28.43 (16.3)		
Return to Normal	Chronic Pain	210	49.19 (27.2)	44.23 (27.3)	103.5	0 (0, 1.7)	49.19 (25.6)	44.35 (24.0)	100.3	0 (0, 1.7)
MID		210			13.6	84.3 (78.6, 88.9)			12.8	88.6 (83.5, 92.5)
MCID (Satisfied)		185	50.08 (27.4)	46.37 (26.7)	30.0	72.4 (65.8, 78.3)	50.08 (26.3)	46.21 (24.5)	31.0	73.3 (44.2, 58.9)
MCID (UnSatisfied)		25	42.60 (24.8)	28.40 (26.9)			42.60 (18.3)	30.60 (12.6)		
OO		210	49.19 (27.2)	44.23 (27.3)	20(10)	92.4 (87.9, 95.6)	49.19 (25.3)	44.35 (23.4)	20(10)	99.5 (54.8, 69)
Return to Normal	Intermittent Pain	210	39.13 (21.7)	47.06 (26.5)	82.5	70 (63.3, 76.1)	39.13 (18.7)	47.66 (20.5)	76.5	80.5 (90.5, 97.4)
MID		210			10.8	90 (85.1, 93.7)			9.3	97.1 (30, 44.1)
MCID (Satisfied)		185	39.60 (21.7)	50.17 (24.9)	37.5	71.4 (64.8, 77.4)	39.60 (19.2)	50.50 (19.1)	40.5	67.1 (84.8, 93.9)
MCID (UnSatisfied)		25	35.58 (21.4)	24.08 (26.6)			35.58 (13.9)	26.69 (17.1)		
OO		210	39.13 (21.7)	47.06 (26.5)	20(10)	92.4 (87.9, 95.6)	39.13 (18.5)	47.66 (19.1)	20(10)	99.5 (60.3, 73.5)

MID = Minimally Important Difference, MCID = Minimally Clinically Important Difference, OO= OMERACT OARSI responder criteria. P(Resp.) = Proportion of Responders.

Table 2: Mean and standard deviation of baseline and change scores estimated using current and multi-level model approaches to responsiveness in patient undergoing total knee replacement in the APEX cohort study. Betas represent the population average characteristic and sigma the estimated standard deviation. Baseline is assumed to be the day of surgery, and change is from 0 to 3 months.

			Current Approaches to Responsiveness				Multi-Level Model Approaches to Responsiveness			
		N	Baseline β_0 σ_{u0}	Change β_1 σ_{u1}	Absolute Threshold	P(Resp.)	Baseline β_0 σ_{u0}	Change β_1 σ_{u1}	Absolute Threshold	P(Resp.)
Return to Normal	Total Pain	190	42.86 (19.7)	31.27 (23.2)	82.3	43.2 (36, 50.5)	42.89 (16.7)	32.09 (17.7)	76.3	51.6 (60.3, 73.5)
MID		190			9.9	79.5 (73, 85)			8.3	93.2 (60.3, 73.5)
MCID (Satisfied)		138	44.09 (19.7)	38.51 (20.6)	22.7	62.6 (55.3, 69.5)	44.13 (16.7)	38.76 (14.7)	29.9	55.3 (66.8, 79.2)
MCID (UnSatisfied)		52	39.62 (19.7)	12.04 (18.0)			39.62 (16.3)	14.28 (11.5)		
Return to Normal	Chronic Pain	190	47.76 (23.6)	31.61 (25.5)	94.9	44.7 (37.5, 52.1)	47.79 (20.5)	32.46 (19.5)	88.7	36.8 (47.9, 62.5)
MID		190			11.8	74.7 (67.9, 80.7)			10.2	90 (47.9, 62.5)
MCID (Satisfied)		138	48.80 (23.4)	38.59 (23.3)	23.7	64.2 (57, 71)	48.88 (20.5)	38.88 (17.7)	30.3	55.3 (47.4, 62)
MCID (UnSatisfied)		52	45.00 (24.1)	13.08 (21.9)			45.00 (20.1)	15.26 (13.3)		
OO		190	47.76 (23.6)	31.61 (25.5)	20(10)	81.0 (74.7, 86.3)	47.78 (20.2)	32.50 (18.9)	20(10)	98.4 (47.9, 62.5)
Return to Normal	Intermittent Pain	190	38.78 (18.2)	30.97 (23.9)	75.3	40.5 (33.5, 47.9)	38.80 (13.8)	31.77 (16.7)	66.4	62.1 (47.9, 62.5)
MID		190			9.1	78.9 (72.5, 84.5)			6.9	94.7 (97.4, 100)
MCID (Satisfied)		138	40.15 (18.3)	38.45 (21.2)	24.8	61.6 (54.3, 68.5)	40.20 (14.1)	38.63 (12.8)	31.2	54.7 (97.4, 100)
MCID (UnSatisfied)		52	35.14 (17.8)	11.12 (19.0)			35.14 (12.8)	13.40 (10.8)		
OO		190	38.78 (18.2)	30.97 (23.9)	20(10)	81.0 (74.7, 86.3)	38.81 (13.6)	31.74 (15.7)	20(10)	98.4 (95.5, 99.7)

MID = Minimally Important Difference, MCID = Minimally Clinically Important Difference, OO= OMERACT OARSI responder criteria. P(Resp.) = Proportion of Responders.

Return To Normal

Using similar baseline score estimates to the conventional RTN approach and different SD's results in a reduction in the threshold of response by approximately 5 points in THR/TKR patients. The change in threshold is due to smaller estimates of baseline and change SD's. When considering the total ICOAP score, the MLM approach classifies approximately 10% more individuals as responders than existing approaches. It is also interesting to note that the threshold of response using the existing approach when considering total ICOAP score in THR patients is beyond the range of the score.

Minimally Important Difference

Using similar change score estimates and different SD's results in an approximately 2 point reduction in the MID threshold in THR/TKR patients. The reduced threshold results in more individuals being classified as responders using the MLM approach.

Minimally Clinically Important Difference

Using the MLM approach in satisfied and unsatisfied individuals results in a small increase in the threshold of response in comparison to existing approaches. The increase in threshold is due to shrunken residuals and therefore reduced the variability of predicted change scores. The increase in threshold results in a reduced number of individuals (3% of THR patients and 6% of TKR patients) being identified as responders.

OMERACT-OARSI

The OO approach uses fixed definitions of responsiveness. Individual estimates of change from the bivariate MLM for constant and intermittent pain are very similar to those from the univariate MLM. However, the standard deviation of the change score is reduced by approximately 0.5 and 1 points in constant and intermittent pain comparing the univariate and bivariate MLM respectively, whereas

the SD of baseline score approximately the same. Despite the larger absolute threshold of 20 and 10 points for changes in 1 or 2 items respectively, i.e. larger than MID, there is an increase in the proportion of individuals identified as responding. The increase is partly due to the use of the relative change threshold, and the reduced variability in change in comparison to the univariate MLM using MID definition of responsiveness.

Responsiveness Classification

The effect of using a MLM approach to defining patient responsiveness compared to existing approaches is presented in Tables 3 and 4 for THR and TKR patients respectively. Whilst the use of MLM provides refined thresholds of responsiveness it fundamentally changes the way individuals are classified due to adjustment for measurement error, regression to the mean and ability to conduct refined tests. Patients previously defined as non-responding using existing methods are now responders (Positive change) in MLM approaches, and similarly, patients defined as responders using existing methods are classified as non-responders (negative change) in MLM, see Figure 3 for graphical illustration. MLM MID and OO methods appear to be most consistent in the reclassification of patients increasing the number of patients defined as non-responders using existing methods as responders in MLM approaches. Whereas MLM RTN and MCII provide a more fundamental change the classifications of patient responsiveness.

Table 3: Cross-classification of responsiveness status in THR patients using existing and MLM model approaches to responsiveness: Return To Normal (RTN), Minimally Important Difference (MID), Minimally Clinical Important Improvement (MCII), and OMERACT OARSI (OO) Criteria.

Total Hip Replacement ICOAP			Multilevel Model							
			RTN		MID		MCII		OO	
			N.Resp	Resp	N.Resp	Resp	N.Resp	Resp	N.Resp	Resp
Existing	Total	N.Resp	**36**	**26**	**5**	**12**	**52**	**7**	-	-
		Resp	**10**	**138**	**0**	**193**	**17**	**134**	-	-
	Chronic	N.Resp	210	0	**24**	**9**	52	6	-	-
		Resp	0	0	**0**	**177**	4	148	-	-
	Intermittent	N.Resp	**33**	**30**	**6**	**15**	50	10	-	-
		Resp	**8**	**139**	**0**	**189**	19	131	-	-
	Chronic & Intermittent	N.Resp	**-**	**-**	**-**	**-**	-	-	**1**	**15**
		Resp	**-**	**-**	**-**	**-**	-	-	**0**	**194**

N.Resp= Non-Responders; Resp = Responders; Bold Cells indicate significance (p<=0.05) of discordant pairs using Exact McNemar test.

Table 4: Cross-classification of responsiveness status in TKR patients using existing and MLM model approaches to responsiveness: Return To Normal (RTN), Minimally Important Difference (MID), Minimally Clinical Important Improvement (MCII), and OMERACT OARSI (OO) Criteria.

Total Knee Replacement ICOAP			Multilevel Model							
			RTN		MID		MCII		OO	
			N.Resp	Resp	N.Resp	Resp	N.Resp	Resp	N.Resp	Resp
Existing	Total	N.Resp	**81**	**27**	**13**	**26**	**64**	**7**	-	-
		Resp	**11**	**71**	**0**	**151**	**21**	**98**	-	-
	Chronic	N.Resp	92	13	**19**	**29**	61	7	-	-
		Resp	28	57	**0**	**142**	24	98	-	-
	Intermittent	N.Resp	**69**	**44**	**9**	**31**	63	10	-	-
		Resp	**3**	**74**	**1**	**149**	23	94	-	-
	Chronic & Intermittent	N.Resp	**-**	**-**	**-**	**-**	-	-	**3**	**33**
		Resp	**-**	**-**	**-**	**-**	-	-	**0**	**154**

N.Resp= Non-Responders; Resp = Responders; Bold Cells indicate significance (p<=0.05) of discordant pairs using Exact McNemar test.

DISCUSSION

The primary purpose of a responsiveness analysis is to convey the variability of an individual's chances of perceiving an improvement following a treatment. Existing approaches appear to be distinct from one another, and the precise relationship between existing methods was unclear.

We have clearly shown how four commonly used approaches to estimating patient responsiveness can be incorporated into the unified statistical framework of MLM. Their translation into unified framework makes many of the assumption (linearity of response, heterogeneity in the timing of measures, multiple measurements) underpinning existing approaches clear. The application of patient responsiveness models in a cohort of orthopaedic patients illustrates how SD's of baseline and change scores in existing approaches are overestimated in comparison to the MLM approach. Thresholds for defining responders from MLM are lower when based on SD, and therefore existing approaches to RTN & MID may appear to provide a worse case scenario with regards the efficacy of a treatment or therapy. Similarly, responsiveness approaches based on the distribution of predicted change scores (MCII) are higher in MLM, and therefore existing thresholds could be described as a best case scenario in comparison to existing approaches. However, the reclassification of patients using the MLM is more fundamental than increasing or reducing the threshold to determine responsiveness, the implicit adjustments for measurement error and regression to the mean change which patients are defined as responding or not.

MLM are not the panacea of patient responsiveness methods, however, they do highlight implicit assumptions in existing approaches and provide sensible adjustments for measurement error, regression to the mean and heterogeneity in the timing of measurements in clinical studies.

From a clinical perspective, it is very clear there are differences in the outcomes at 3 months following THR and TKR. Whilst patient's baseline level of pain, are similar between THR and TKR, the response to surgery is less, and consistently less (lower variability) for all pain domains. Similarly, we

have previously observed different patterns of pain, in relation to pain at rest and pain on movement,[60] yet the mechanisms underpinning theses effects are unclear and require more research, but this does emphasize the necessity to treat hip and knee osteoarthritis as separate disease states.

Strengths & Limitations

One of the key benefits of adopting a MLM approach when defining clinically meaningful change is the improved estimation of individual change by the greater flexibility in the MLM framework. Specifically, MLM do not assume the response is measured without error, they adjust for regression to the mean, the trajectory of recovery is not constrained to be linear, and data from multiple measurements and variability in the timing of those measurement occasions can also be incorporated into the model. Furthermore, assuming the underlying MLM adequately represents the true causal mechanism, parameter estimates, SD's and standard errors will be unbiased in comparison to existing approaches.

Furthermore, the unification of existing approaches into a MLM framework clearly shows the relationship between the four different approaches. For example, RTN and MID share the same underlying model. MCII is also the same at RTN/MID if you assume the baseline and change scores are the same across strata of un/satisfied patients. Similarly, the model underlying OO approach is the same as the RTN/MID approach if you assume independence in the measured outcomes of the two trajectories, and the error term.

Despite the numerous benefits of adopting a MLM approach, it is not to say it is without some limitations. MLM are technically more demanding than existing formulations of patient responsiveness, and whilst there are no theoretical limits on how large or small samples have to be, model convergence is not guaranteed. The need to use appropriate estimation methods[38] or denominator degrees of freedom[55] when calculating standard errors also requires consideration.

Furthermore, it is important to perform model diagnostic to check the data fit with the model. MLM does not improve the arbitrary placement of the thresholds that define responsiveness in comparison to existing methods, and despite the improved trajectory modelling, it is currently unclear if the refined definitions correlate more strongly with patient expectations, functional data, long-term self-reported outcomes, or hard end-points such as mortality and revision. Further research externally validating the classification using patient groups, expert opinion[61] or functional data may demonstrate improved classification of those responding to treatment in comparison to existing methods. In addition, the use of multiple measurements in MLM primarily restricts the method to a research setting.

It is clear the MLMs provide considerable advantages over existing approaches to identifying patients who respond to a treatment. Consequently, the proportion of individuals thought not to be responding to treatment may be smaller than previously thought. Using the redefined definition may reduce the number of individuals misclassified as non-responders, and improve the prediction of those individuals who are likely to respond to treatment.

Figures

Figure 1: Illustration of a “double” long data setup for creating a bivariate MLM.

Figure 2: Modelling diagnostic plots. Upper left, ladder plot of observed ICOAP total scores at 0, 3, 6, and 12 months following THR, and population average trajectory estimated from a MLM, used in RTN and MID analysis, with 2 linear splines with a knot at 3 months. Upper right, lower left and right plots are quantile-quantile plots of the residual distribution of random effects estimated from a MLM with 2 linear splines with a knot at 3 months.

Figure 3: Change in Responder classification using a RTN definition comparing existing approaches to MLM approach using the ICOAP total score in patients following THR. Upper Left panel illustrates observed trajectories for patients whose responsiveness classification changes using a MLM approach to estimating responsiveness. Lower left panel illustrates the observed and predicted trajectories of ICOAP total score in patients positively reclassified as responders compared to existing approaches. Lower right panel illustrates the observed and predicted trajectories of ICOAP total score in patients negatively reclassified as non-responders compared to existing approaches.

Abbreviations

APEX – Arthroplasty Pain Experience

ICOAP - Intermittent and Constant Osteoarthritis Pain

MCII – Minimally Clinical Important Improvement

MID – Minimal Important Difference

MLM – Multi Level Model

OO – OMERACT OARSI Criteria

RCI – Relative Change Index

RTN – Return To Normal

SD – Standard Deviation

SE – Standard Error

THR – Total Hip Replacement

TKR – Total Knee Replacement

Acknowledgements

We would like to thank Professor Fiona Steele for her extensive comments and help preparing this manuscript.

Author Contributions

Study Conception (AS). APEX study design (VW, RGH, AWB). APEX acquisition of data (VW, RGH, AWB, EL). ACHE study design (JD, DB, AP). Wrote first draft & revised manuscript (AS). Drafting and review of the manuscript (AS, VW, RGH, AWB, EL, JD, DB, AP). Final approval of Manuscript (AS, VW, RGH, AWB, EL, JD, DB, AP)

Funding Statement

This work was supported by AS is funded by an MRC Fellowship MR/L01226X/1 and HTA Project:11/63/01 – 'ACHE'. This article presents independent research funded by the National Institute for Health Research (NIHR) under its Programme Grants for Applied Research programme (RP-PG-0407-10070). The views expressed in this article are those of the authors and not necessarily those of the NHS, the NIHR or the Department of Health. The research team acknowledges the support of the NIHR, through the Comprehensive Clinical Research Network.

Competing Interest

The Authors have no competing interests to declare.

Data Sharing

No data is available to be shared.

REFERENCES

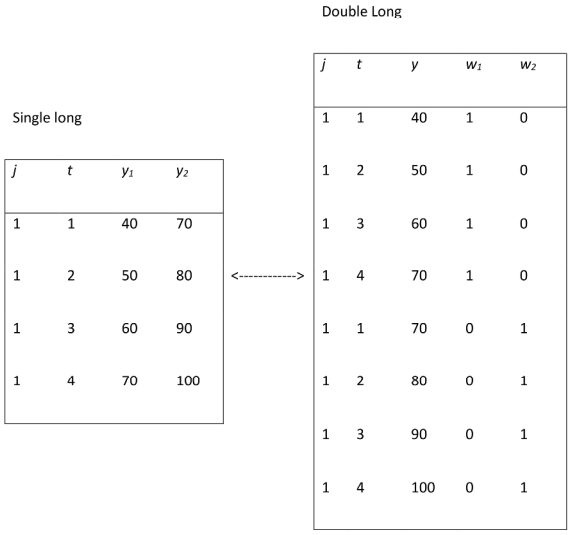
1. Felson DT, Naimark A, Anderson J, et al. The prevalence of knee osteoarthritis in the elderly. The Framingham Osteoarthritis Study. *Arthritis and rheumatism* 1987;30(8):914-8. [published Online First: 1987/08/01]
2. Lawrence RC, Felson DT, Helmick CG, et al. Estimates of the prevalence of arthritis and other rheumatic conditions in the United States. Part II. *Arthritis and rheumatism* 2008;58(1):26-35. doi: 10.1002/art.23176
3. National Joint Registry. 10th Annual Report 2013. Hemel Hempstead2013.
4. Beswick AD, Wylde V, Gooberman-Hill R, et al. What proportion of patients report long-term pain after total hip or knee replacement for osteoarthritis? A systematic review of prospective studies in unselected patients. *Bmj Open* 2012;2(1) doi: ARTN e000435

DOI 10.1136/bmjopen-2011-000435
5. Jeffery AE, Wylde V, Blom AW, et al. "It's there and I'm stuck with it": patients' experiences of chronic pain following total knee replacement surgery. *Arthritis care & research* 2011;63(2):286-92. doi: 10.1002/acr.20360
6. Kassam A, Dieppe P, Toms AD. An analysis of time and money spent on investigating painful Total Knee Replacements. *British Journal of Medical Practitioners* 2012;5(3)
7. Bellamy N, Buchanan WW, Goldsmith CH, et al. Validation study of WOMAC: a health status instrument for measuring clinically important patient relevant outcomes to antirheumatic drug therapy in patients with osteoarthritis of the hip or knee. *The Journal of rheumatology* 1988;15(12):1833-40.
8. Klassbo M, Larsson E, Mannevik E. Hip disability and osteoarthritis outcome score. An extension of the Western Ontario and McMaster Universities Osteoarthritis Index. *Scandinavian journal of rheumatology* 2003;32(1):46-51.
9. Roos EM, Roos HP, Lohmander LS, et al. Knee Injury and Osteoarthritis Outcome Score (KOOS)--development of a self-administered outcome measure. *The Journal of orthopaedic and sports physical therapy* 1998;28(2):88-96. doi: 10.2519/jospt.1998.28.2.88
10. Dawson J, Fitzpatrick R, Carr A, et al. Questionnaire on the perceptions of patients about total hip replacement. *J Bone Joint Surg Br* 1996;78B(2):185-90.
11. Dawson J, Fitzpatrick R, Murray D, et al. Questionnaire on the perceptions of patients about total knee replacement. *J Bone Joint Surg Br* 1998;80B(1):63-69. doi: Doi 10.1302/0301-620x.80b1.7859
12. Focht BC, Rejeski WJ, Ambrosius WT, et al. Exercise, self-efficacy, and mobility performance in overweight and obese older adults with knee osteoarthritis. *Arthritis and rheumatism* 2005;53(5):659-65. doi: 10.1002/art.21466
13. Smith AJ, Dieppe P, Howard PW, et al. Failure rates of metal-on-metal hip resurfacings: analysis of data from the National Joint Registry for England and Wales. *Lancet* 2012;380(9855):1759-66. doi: 10.1016/s0140-6736(12)60989-1
14. Smith AJ, Dieppe P, Porter M, et al. Risk of cancer in first seven years after metal-on-metal hip replacement compared with other bearings and general population: linkage study between the National Joint Registry of England and Wales and hospital episode statistics. *Bmj* 2012;344:e2383. doi: 10.1136/bmj.e2383
15. Hunt LP, Ben-Shlomo Y, Clark EM, et al. 45-day mortality after 467 779 knee replacements for osteoarthritis from the National Joint Registry for England and Wales: an observational study. *Lancet* 2014 doi: 10.1016/s0140-6736(14)60540-7

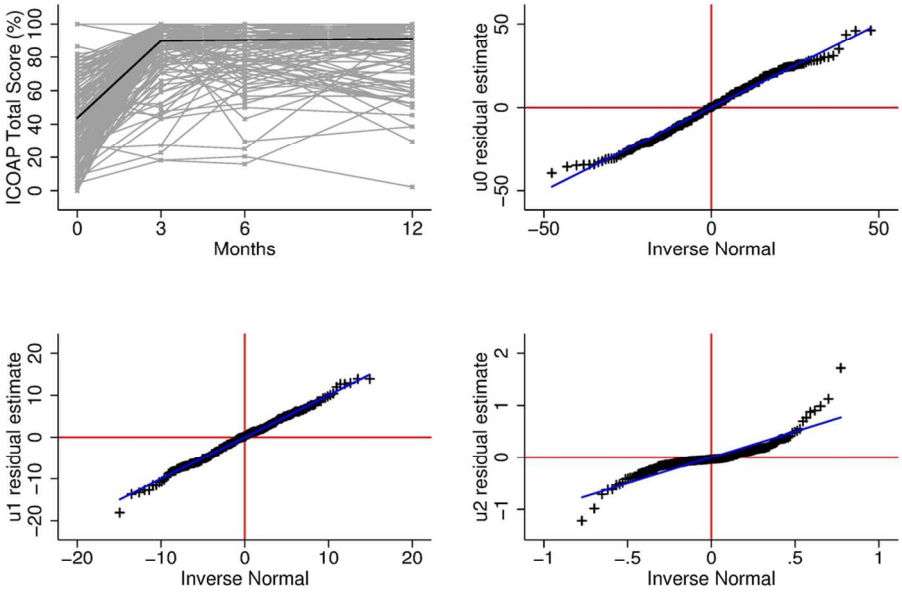
16. Hunt LP, Ben-Shlomo Y, Clark EM, et al. 90-day mortality after 409,096 total hip replacements for osteoarthritis, from the National Joint Registry for England and Wales: a retrospective analysis. *Lancet* 2013;382(9898):1097-104. doi: 10.1016/s0140-6736(13)61749-3
17. Riddle DL, Stratford PW, Bowman DH. Findings of extensive variation in the types of outcome measures used in hip and knee replacement clinical trials: A systematic review. *Arthrit Rheum-Arthr* 2008;59(6):876-83. doi: Doi 10.1002/Art.23706
18. Wylde V, Bruce J, Beswick A, et al. Assessment of chronic postsurgical pain after knee replacement: a systematic review. *Arthritis care & research* 2013;65(11):1795-803. doi: 10.1002/acr.22050
19. Wylde V, Blom AW. The failure of survivorship. *The Journal of bone and joint surgery British volume* 2011;93(5):569-70. doi: 10.1302/0301-620X.93B5.26687 [published Online First: 2011/04/23]
20. Darzi. High quality care for all: NHS Next Stage Review final report, 2008.
21. Hawker GA, Davis AM, French MR, et al. Development and preliminary psychometric testing of a new OA pain measure--an OARSI/OMERACT initiative. *Osteoarthritis and cartilage / OARS, Osteoarthritis Research Society* 2008;16(4):409-14. doi: 10.1016/j.joca.2007.12.015
22. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. *Acta Psychiatr Scand* 1983;67(6):361-70.
23. Williams A, Kind P. The present state of play about QALYs. In: Hopkins A, ed. Measure of the quality of life: the uses to which they may be put: RCP publications 1992.
24. Christensen L, Mendoza JL. A Method of Assessing Change in a Single Subject - an Alteration of the Rc Index. *Behav Ther* 1986;17(3):305-08. doi: Doi 10.1016/S0005-7894(86)80060-0
25. Guyatt GH, Osoba D, Wu AW, et al. Methods to explain the clinical significance of health status measures. *Mayo Clinic proceedings* 2002;77(4):371-83. doi: 10.1016/S0025-6196(11)61793-X
26. Jacobson NS, Roberts LJ, Berns SB, et al. Methods for defining and determining the clinical significance of treatment effects: description, application, and alternatives. *Journal of consulting and clinical psychology* 1999;67(3):300-7.
27. Jacobson NS, Truax P. Clinical significance: a statistical approach to defining meaningful change in psychotherapy research. *Journal of consulting and clinical psychology* 1991;59(1):12-9.
28. Kvien TK, Heiberg T, Hagen KB. Minimal clinically important improvement/difference (MCII/MCID) and patient acceptable symptom state (PASS): what do these concepts mean? *Annals of the rheumatic diseases* 2007;66 Suppl 3:iii40-1. doi: 10.1136/ard.2007.079798
29. Maksymowych WP, Richardson R, Mallon C, et al. Evaluation and validation of the patient acceptable symptom state (PASS) in patients with ankylosing spondylitis. *Arthritis and rheumatism* 2007;57(1):133-9. doi: 10.1002/art.22469
30. Norman GR, Sloan JA, Wyrwich KW. Interpretation of changes in health-related quality of life: the remarkable universality of half a standard deviation. *Medical care* 2003;41(5):582-92. doi: 10.1097/01.MLR.0000062554.74615.4C
31. Norman GR, Sridhar FG, Guyatt GH, et al. Relation of distribution- and anchor-based approaches in interpretation of changes in health-related quality of life. *Medical care* 2001;39(10):1039-47.
32. Pham T, van der Heijde D, Altman RD, et al. OMERACT-OARSI initiative: Osteoarthritis Research Society International set of responder criteria for osteoarthritis clinical trials revisited. *Osteoarthritis and cartilage / OARS, Osteoarthritis Research Society* 2004;12(5):389-99. doi: 10.1016/j.joca.2004.02.001
33. Revicki D, Hays RD, Cella D, et al. Recommended methods for determining responsiveness and minimally important differences for patient-reported outcomes. *Journal of clinical epidemiology* 2008;61(2):102-9. doi: 10.1016/j.jclinepi.2007.03.012
34. Tubach F, Ravaud P, Baron G, et al. Evaluation of clinically relevant changes in patient reported outcomes in knee and hip osteoarthritis: the minimal clinically important improvement. *Annals of the rheumatic diseases* 2005;64(1):29-33. doi: 10.1136/ard.2004.022905

35. Tubach F, Ravaud P, Baron G, et al. Evaluation of clinically relevant states in patient reported outcomes in knee and hip osteoarthritis: the patient acceptable symptom state. *Annals of the rheumatic diseases* 2005;64(1):34-7. doi: 10.1136/ard.2004.023028
36. Judge A, Cooper C, Williams S, et al. Patient-reported outcomes one year after primary hip replacement in a European Collaborative Cohort. *Arthritis care & research* 2010;62(4):480-8. doi: 10.1002/acr.20038
37. Goldstein H. Multilevel Statistical Models2002.
38. Browne WJ, Draper D. Implementation and performance issues in the Bayesian and likelihood fitting of multilevel models. *Computation Stat* 2000;15(3):391-420. doi: DOI 10.1007/s001800000041
39. King MT. A point of minimal important difference (MID): a critique of terminology and methods. *Expert Rev Pharmacoecon Outcomes Res* 2011;11(2):171-84. doi: 10.1586/erp.11.9
40. Schuck P, Zwingmann C. The 'smallest real difference' as a measure of sensitivity to change: a critical analysis. *Int J Rehabil Res* 2003;26(2):85-91. doi: 10.1097/01.mrr.0000070759.63544.65
41. Wylde V, Gooberman-Hill R, Horwood J, et al. The effect of local anaesthetic wound infiltration on chronic pain after lower limb joint replacement: a protocol for a double-blind randomised controlled trial. *BMC musculoskeletal disorders* 2011;12:53. doi: 10.1186/1471-2474-12-53
42. Altman DG, Gore SM, Gardner MJ, et al. Statistical guidelines for contributors to medical journals. *British medical journal* 1983;286(6376):1489-93.
43. Sterne JA, Davey Smith G. Sifting the evidence-what's wrong with significance tests? *Bmj* 2001;322(7280):226-31.
44. McConnell S, Kolopack P, Davis AM. The Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC): A review of its utility and measurement properties. *Arthrit Rheum-Arthr* 2001;45(5):453-61. doi: Doi 10.1002/1529-0131(200110)45:5<453::Aid-Art365>3.0.Co;2-W
45. Twisk J, Rijmen F. Longitudinal tobit regression: A new approach to analyze outcome variables with floor or ceiling effects. *Journal of clinical epidemiology* 2009;62(9):953-58. doi: DOI 10.1016/j.jclinepi.2008.10.003
46. Ram N, Grimm KJ. Growth mixture modeling: A method for identifying differences in longitudinal change among unobserved groups. *Int J Behav Dev* 2009;33(6):565-76. doi: Doi 10.1177/0165025409343765
47. Jones G, Lyons P. Approximate graphical methods for inverse regression. *Journal of Data Science* 20009;7:61-72.
48. Snijders TAB, Bosker RJ. Multilevel Analysis: An Introduction to Basic and Advanced Multilevel Modeling, second edition. London: Sage Publishers 2012.
49. Fieuws S, Verbeke G. Pairwise fitting of mixed models for the joint modeling of multivariate longitudinal profiles. *Biometrics* 2006;62(2):424-31. doi: 10.1111/j.1541-0420.2006.00507.x
50. Fieuws S, Verbeke G. Joint modelling of multivariate longitudinal profiles: pitfalls of the random-effects approach. *Statistics in medicine* 2004;23(20):3093-104. doi: 10.1002/sim.1885
51. Verbeke G, Molenberghs G. Linear mixed models for longitudinal data. USA: Springer 2000.
52. Rasbash J, Steele F, Browne WJ, et al. A user's guide to MLwIN. UK2009.
53. Copas JB. Regression, Prediction and Shrinkage. *J R Stat Soc B* 1983;45(3):311-54.
54. Fitzmaurice GM, Laird NM, Ware JH. Applied Longitudinal Analysis. USA: Wiley 2004.
55. Kenward MG, Roger JH. Small sample inference for fixed effects from restricted maximum likelihood. *Biometrics* 1997;53(3):983-97.
56. Pan HQ, Goldstein H. Multi-level repeated measures growth modelling using extended spline functions. *Statistics in medicine* 1998;17(23):2755-70. doi: Doi 10.1002/(Sici)1097-0258(19981215)17:23<2755::Aid-Sim41>3.0.Co;2-E

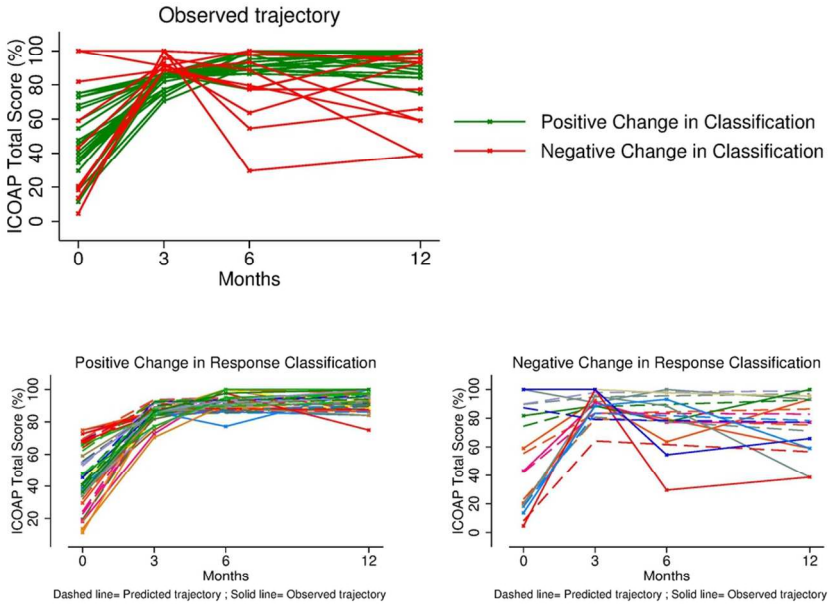
57. Rabe-Hesketh S, Skrondal A. Multilevel and latent variable modeling with composite links and exploded likelihoods. *Psychometrika* 2007;72(2):123-40. doi: DOI 10.1007/s11336-006-1453-8
58. Nagin DS, Odgers CL. Group-Based Trajectory Modeling in Clinical Research. *Annu Rev Clin Psycho* 2010;6:109-38. doi: DOI 10.1146/annurev.clinpsy.121208.131413
59. Lenguerrand E, Wylde V, Gooberman-Hill R, et al. Trajectories of Pain and Function after Primary Hip and Knee Arthroplasty: The ADAPT Cohort Study. *PLoS One* 2016;11(2):e0149306. doi: 10.1371/journal.pone.0149306
60. Sayers A, Wylde V, Lenguerrand E, et al. Rest Pain and Movement-Evoked Pain as Unique Constructs in Hip and Knee Replacements. *Arthritis care & research* 2016;68(2):237-45. doi: 10.1002/acr.22656
61. Bellamy N, Carette S, Ford PM, et al. Osteoarthritis antirheumatic drug trials. III. Setting the delta for clinical trials--results of a consensus development (Delphi) exercise. *The Journal of rheumatology* 1992;19(3):451-7.



296x419mm (300 x 300 DPI)



101x73mm (300 x 300 DPI)



101x73mm (300 x 300 DPI)

```
*******************************************************************************
*  A unified multi-level model approach to assessing patient responsiveness
*  including; return to normal, minimally important differences, and minimally
*  clinical important differences for patient reported outcome measures.
*******************************************************************************
*
*  Sayers A*, Wylde V, Lenguerrand E, Gooberman-Hill R, Dawson J, Beard D,
*  Price A, Blom AW
*
*  1.   Musculoskeletal Research Unit, School of Clinical Sciences,
*       University of Bristol, Southmead Hospital, Westbury On Trym,
*              Bristol, BS10 5NB.
*  2.   Nuffield Department of Population Health, University of Oxford,
*              Old Road Campus, Headington, Oxford OX3 7LF, UK
*  3.   Biomedical Research Unit, Nuffield Department of Orthopaedics,
*              Rheumatology and Musculoskeletal Science, Nuffield Orthopaedic Centre,
*              Windmill Road, Oxford, OX2 9JA
*
*      Address for Correspondence
*   Adrian Sayers, Musculoskeletal Research Unit, School of Clinical Sciences,
*   University of Bristol, Learning and Research Building (Level 1),
*   Southmead Hospital, Westbury on Trym, Bristol, BS10 5NB
*
*
*   E-mail: adrian.sayers@bristol.ac.uk
*   Tel: 44 (0)117 4147880; Fax + 44(0)117 414 7924
*******************************************************************************
* Abstract
* Stata code to illustrate calculation of patient reponsiveness using existing
* and multi-level model methods.
* Do file should be run comlpletely inorder to simulate data from a linear model
* and perform calculations.
* File requires MLWin and copy of runmlwin downloaded for Stata.

*******************************************************************************
* 1. Simulate a dataset
*******************************************************************************
{
* Design matrix in OO Format
set seed 111
clear
set obs 100
gen id= _n

* Set Parameters values
       * Set Fixed Effect Parameters
       local b0 = 49.19
              local b1 = 44.35 / 3
                     local b2 = 39.12
```

```
                        local b3 = 47.66 / 3
* Set Random Effect Standard Deviations & Correlation Matrix
local u0 = 25.3
        local u1 = 23.4 / 3
                local u2 = 18.5
                        local u3 = 19.1 / 3
                                matrix u = (`u0',`u1',`u2',`u3')'
                                        matrix u_corr = (1   ,0.3 ,0.1 ,0.1 \  ///
                                                         0.3 ,1   ,0.1 ,0.1 \  ///
                                                         0.1 ,0.1 ,1   ,0.3 \  ///
                                                         0.1 ,0.1 ,0.3 ,1   )
* Draw Random Parameters
        drawnorm u0 u1 u2 u3 , sds(u) corr(u_corr)


* Create 4 measurement occassions
expand 4
by id , sort : gen t = _n-1

* Prepare for a reshape into double long
gen _1= 1
        gen _2= 1
                reshape long _ , i(id t) j(resp)
                        drop _

* Set error Standard Deviations & Correlation Matrix
local e1= 5
        local e2= 5
                matrix e = (`e1', `e2')'
                        matrix e_corr = (1   ,0.1 \  ///
                                         0.1 ,1   )  //

                                drawnorm e1 e2 , sds(e) corr(e_corr)


* Create response indicators for OO
gen w1 = 1 if resp==1
        replace w1 = 0 if resp==2
                gen w2 = 0 if resp==1
                        replace w2 = 1 if resp==2

* Generate a satisfaction indicator, uncorrelated with effects just for illustration
gen x = cond(uniform()>=0.3,1,0) if resp==1 & t==1
        by id : egen _x = min(x)
                *Create dummy variables
                        gen x1 = 1 if _x==1
                                replace x1 = 0 if _x==0
                                        gen x2 = 0 if _x==1
                                                replace x2 = 1 if _x==0
```

```
                                                drop x _x


* Predict response
gen y = (`b0' + u0)* w1 + (`b1' + u1)* w1 * t + e1* w1 + ///
               (`b2' + u2)* w2 + (`b3' + u3)* w2 * t + e2* w2 //

tempfile simdata
       save `simdata' , replace

}
*******************************************************************************
* 2.1 Existing Methods (n.b. only for first response)
*******************************************************************************
use  `simdata' , clear
       * Working with the first and last measurment occassion
              keep if  t ==0 | t==3
                     sort id resp t
                            by id resp : gen d_y = y[_n] - y[_n-1]
*********************
* 2.1.1 Existing RTN
*********************
{
       sum y if t==0 & resp==1
              local rtn = r(mean) + 2*r(sd)
                     by id resp: gen ex_rtn =cond(y>=`rtn',1 ,0) if _n==2 & resp==1
                            by id resp: gen ex_rci = cond((d_y / sqrt(2*(`r(sd)' * sqrt(1-0.9))^2))>=1.96,1,0) if _n==2 & resp==1
                                   by id resp: gen ex_rtn_rci = cond(ex_rtn==1 & ex_rci==1 ,1,0) if _n==2 & resp==1

                                   tab ex_rtn if resp==1         // Number of individuals returning to normal
                                   tab ex_rci if resp==1         // Number of individuals significant change
                                   tab ex_rtn_rci if resp==1     // Number of individuals significant change & returning to normal
                                   }
*********************
* 2.1.2 Existing MID
*********************
{
sum y if t==0 & resp==1
       local mid = r(sd)*0.5
              by id resp : gen ex_mid =cond(d_y>=`mid',1,0)  if _n==2 & resp==1

                     tab ex_mid if resp==1         // Number of individuals with minimally important difference
}
*********************
* 2.1.3 Existing MCID
* n.b using the 25th centile is pain is reverse coded.
*********************
{
centile d_y if resp==1 & x1==1 , c(25)
```

```
        local mcid = r(c_1)
                by id resp: gen ex_mcid = cond(d_y>=`mcid',1,0) if _n==2 & resp==1

                        tab ex_mcid if resp==1        // Number of individuals meeting the MCID criteria
}

*******************************
* 2.1.4 Existing (OO) OMERACT-OARSI
*******************************
{
* 50% relative, 20% absolute single
* 20% relative, 10% absolute both

* Calculate Relative Change
        by id resp: gen d_rely= (d_y/y[_n-1])*100
                * Mark Single Changes
                        by id resp: gen ex_oo_single =1 if (d_y>=20 & d_y<.) | (d_rely>=50 & d_rely<.) & _n==2
                                * Mark Double Changes
                                        by id resp: gen ex_oo_double =1 if (d_y>=10 & d_y<.) | (d_rely>=20 & d_rely<.) & _n==2
                                                * Sum double changes
                                                        by id  : egen ex_oo_double_sum = total(ex_oo_double) if  d_y!=.

* Mark OO criteria
        by id : gen _ex_oo = cond(ex_oo_single==1 | ex_oo_double_sum==2 , 1,0) if d_y!=.
                by id : egen ex_oo = max(_ex_oo) if d_y!=.

                tab ex_oo if resp==1   // Number of individuals meeting the oo criteria
}
*******************************************************************************
* 2.2 Multi-level Methods
*******************************************************************************
// Set the global macro to identify the location and version of mlwin
global MLwiN_path "C:\Program Files (x86)\MLwiN v2.36\i386\MLwiN.exe"
        use  `simdata' , clear
                keep if resp==1
* Create a constant
gen cons=1

******************
* 2.2.1 MLM RTN / MID Model
******************
{
*                       0-----------------1
*                       1,2,3,4,5,6,7,8,9,0,1,2,3,4,5,6,7,8,9,0,
matrix a = (1,1,1)

runmlwin y cons t if resp==1 ,                                                          /// Fixed effect
        level1(t: cons, residuals(_e, )  )                                  /// Level 1 variance
                level2(id: cons t, elements(a) residuals(_u, ) )     /// Level 2 varaince
```

```
                    maxiterations(10)  corr sd nopause                          //      Modelling options

* Predict Individual effects
gen xb_fe =  _b[cons] + _b[t]*t
       gen xb_re =  _u0 + _u1*t
              gen xb = xb_fe + xb_re

* Predict to asses responsiveness at (3month)
gen xb_t =  (_b[cons]+_u0) + (_b[t]+_u1)*3

* RTN threshold
local mlm_rtn = _b[FP1:cons] + 2*(_b[RP2:var(cons)]^0.5)

* Mark RTN
gen mlm_rtn = cond(xb_t>=`mlm_rtn',1,0)

* Calculate RCI
       gen xb_d = _b[FP1:t] + _u1
              gen se_d = (_se[FP1:t]^2 +_u1se^2)^0.5
                     gen z_d = xb_d / se_d

* Mark RCI
gen mlm_rci = cond(z_d>=1.96,1,0)

* Mark RTN RCI composite
gen mlm_rtn_rci = cond(mlm_rtn==1 & mlm_rci==1, 1, 0)
       egen pickone = tag(id)

              tab mlm_rtn_rci if pickone==1 // Number of individuals meeting the MLM RTN RCI  criteria
}
**********************
* 2.2.2 MLM MID
**********************
{
* MID Threshold @ 3 months
local mlm_mid = 0.5*(_b[RP2:var(cons)]^0.5)
       gen mlm_mid = cond( (_b[t]+_u1)*3>= `mlm_mid' ,1 ,0 )
              tab mlm_mid if pickone==1 // Number of individuals meeting the MLM MID criteria

* Drop previous residual and predictions
drop  _u0 _u1 _u0se _u1se _e0 _e0se  xb_fe xb_re xb xb_t xb_d se_d z_d
}
********************
* 2.2.3  MLM MCID
********************
{
* Stratify intercept and slope by satisfaction
gen consx1= cons*x1
       gen consx2 = cons*x2
```

```
                gen tx1 = t*x1
                        gen tx2 = t*x2

* Specify RE variance matrix
*                       0-----------------1-------------------2
*                       1,2,3,4,5,6,7,8,9,0,1,2,3,4,5,6,7,8,9,0,1
matrix u = (1,1,1,0,0,1,0,0,1,1)

* Specify RE variance matrix
*                       0-----------------1-------------------2
*                       1,2,3,4,5,6,7,8,9,0,1,2,3,4,5,6,7,8,9,0,1
matrix e = (1,0,1)

runmlwin y consx1 tx1 consx2 tx2 if resp==1 ,                                                                   /// Fixed effect
        level1(t: consx1 consx2, elements(e)  residuals(_e, norecode ))                         /// Level 1 variance
                level2(id: consx1 tx1 consx2 tx2 ,elements(u)  residuals(_u, norecode ))   /// Level 2 varaince
                        maxiterations(10)  corr sd nopause                                                              //      Modelling
options

* Estimate the Change  for all individuals
gen xb_slope = (_b[tx1]+_u1)*x1 + (_b[tx2]+_u3)*tx2

* Find the 75th (inverse coding 25th) centile of those satisfied
centile xb_slope if tx1==3 , c(25)
        local mlm_mcid = r(c_1)

*tag observations which have improvements greater than mcid
        gen mlm_mcid = cond(xb_slope>=`mlm_mcid',1,0) if t==3
                tab mlm_mcid if t==3 // Number of individuals meeting the MCID  criteria
        }
*********************
* 2.2.4  MLM (OO) OMERACT-OARSI
*********************
{
* 50% relative, 20 absolute single assuming a 0-100 score
* 20% relative, 10 absolute both assuming a 0-100 score
use  `simdata' , clear
        sort id t resp


* Create response indicators
gen cons =1
        gen consw1 = cons*w1
                gen consw2 = cons*w2
                        gen tw1 = t*w1
                                gen tw2 = t*w2

runmlwin y  consw1 tw1 consw2  tw2 ,                                                                    /// Fixed Effect
        level1(resp:)                                                                                   /// Level 1 variance
```

```
        level2(t: consw1 consw2,  residuals(_e, norecode ))                              /// Level 2 variance
                level3(id: consw1 tw1 consw2 tw2 , residuals(_u, norecode ))        /// Level 3 varaince
                        maxiterations(10)  corr sd nopause                                                      //      Modelling options

* Calculate predicted changes
gen mlm_d = (_b[tw1] + _u1 )*tw1  + (_b[tw2] + _u3 )*tw2
        gen mlm_bl = (_b[consw1] + _u0)*consw1 + (_b[consw2] + _u2)*consw2
                gen mlm_relyd=  (mlm_d /mlm_bl)*100

* Mark out responders
                        by id resp ,sort: gen mlm_oo_single =1 if (( mlm_d>=20 & mlm_d<.) | (mlm_relyd>=50 & mlm_relyd<.)) & t==3
                                * Mark Double Changes
                                        by id resp ,sort: gen mlm_oo_double =1 if ((mlm_d>=10 & mlm_d<.) | (mlm_relyd>=20 & mlm_relyd<.)) & t==3
                                                * Sum double changes
                                                        by id ,sort  : egen mlm_oo_double_sum = total(mlm_oo_double) if t==3

* Mark OO criteria
by id : gen _mlm_oo = cond(mlm_oo_single==1 | mlm_oo_double_sum==2 , 1,0) if t==3
        by id : egen mlm_oo = max(_mlm_oo) if t==3

                tab mlm_oo if resp==1  // Number of individuals meeting the MLM OO criteria
}
```