More efficient DMOAD trials via innovative screening strategies

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Background
The number of patients to recruit for assessing effectiveness of DMOAD in RCTs depends on the proportion of progressors in the population. Progressors in general OA population: 10-30%[1] ⇒ large cohorts, long / expensive RCTs.

Low Progressor Proportion: Larger Sample Size

High Progressor Proportion: Smaller Sample Size

Objectives
Use predictive modeling and cartilage degradation markers to:
1 Screen patients,
2 Make individual predictions about future progression,
3 Recruit a progressor-enriched cohort
4 Achieve same / better success rate with smaller cohorts / lower budgets

Method – Progression Modeling
First challenge: Build predictive models (regularized logistic regressions) of progression over 30M based on biomarkers:
- based on Coll2-1 (see graphs below)
- based on both Coll2-1 and Coll2-1-NO2
Moderate AUC of 60 to 65% is obtained through cross-validation.

Method – Trial Optimization
Second challenge: Use the model and study design parameters to optimize trial.

Hypotheses to play with:
- Natural progressor rate in general OA population: 10 to 20%
- Expected drug effect: 30 to 50%
- Costs of the trial (cost of a screening visit, cost of other visits, cost of IMP, cost of Imaging, etc.).
- Extra cost of the biomarker testing.

⇒ Optimize overall cost by playing with progression model cutoff, i.e. find optimal balance
  - between sensitivity and specificity,
  - between number of patients screened and number of patients actually enrolled.

Increase model threshold ⇒ More progressor-enriched cohort, but lots of patients screened and not enrolled.

Decrease model threshold ⇒ Less progressor-enriched, but fewer patients screened and not enrolled.

Results
Gain up to 30% cost reduction and 40% sample size reduction.

Example:
- Natural progressor rate: 20%;
- Actual effect of DMOAD to be tested: 50%.
- Study design: 6 visits (screening, follow-up, final), 2 x-rays, 2 MRIs.

Hypotheses have been made about item costs according to Belgian practice.

Conclusions
Shows interest for biomarker-based OA-progressors cohort enrichment.
Simplifies potential gains for the conduct of RCTs.
Results should be replicated on other, more representative cohorts.
Additional markers / clinical factors could be considered for the models.

References
[3] Ornetti et al., 2009; OARSI-OMERACT

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