# The journey of innovation

## of qualification of novel methodologies

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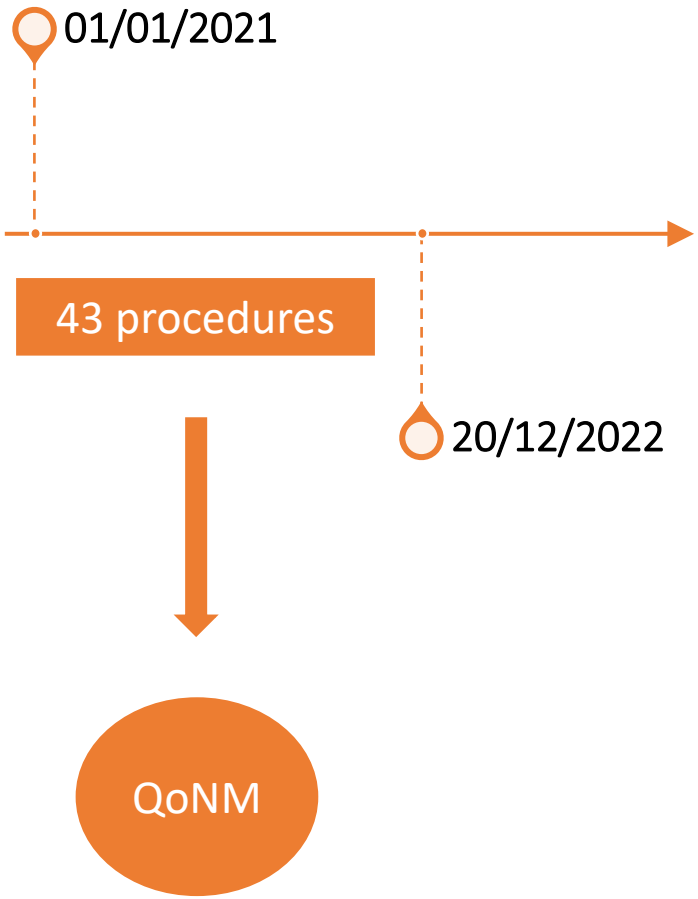
# Background

Qualification Opinion (QO) - it is considered that the proposed method is an acceptable regulatory standard for the **defined context of use** in drug development and shall be used by all stakeholders enabling more efficient developments.

The aim of this analysis is to:

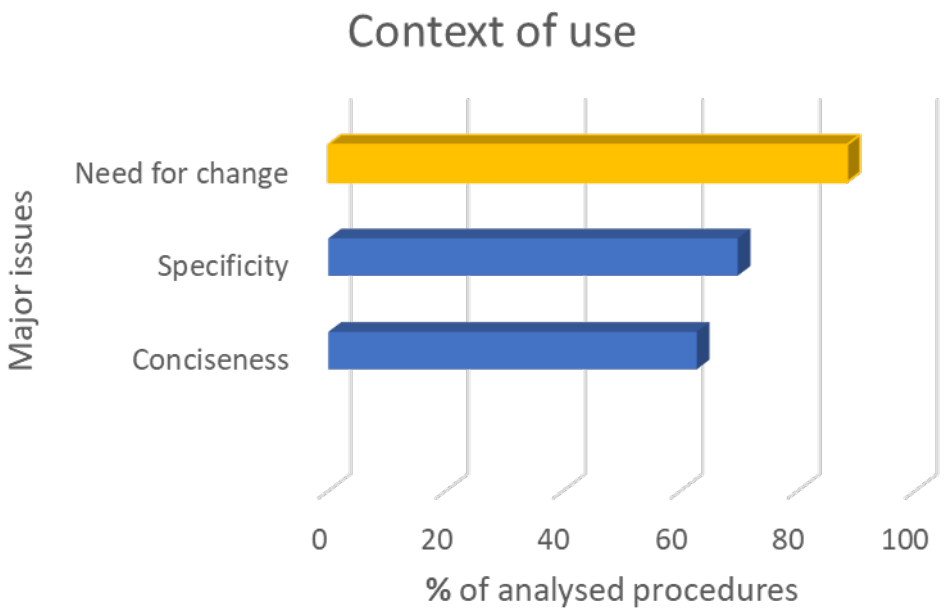
- analyse the latest Qualifications of Novel Methodologies (QoNM) submissions
- examine related publications, patents and clinical trials within the qualified context of use
- demonstrate the journey of qualification procedures from early concepts towards accepted regulatory standards




## 3 main tasks/findings:

- **Context of use (CoU):** A table has been created describing each qualification procedure, it's context of use (intended and approved), list of issues and search results.
- **Lists of issues** have been summarized into categories.
- **A set of keywords based on the CoU** was used for the **search** of clinical trials, publications and patents related to the QoNM and the approved context of use.

ClinicalTrials.gov
PubMed (nih.gov)
Espacenet – patent search




The objective is to seek CHMP qualification for the proposed statistical methodology intended to improve the efficiency of Phase 2 and 3 clinical trials, by using trial subjects' predicted outcomes on placebo (prognostic scores) in linear covariate adjustment; **such prognostic scores can be generated using a predictive model trained on historical data. Our approach is efficient in the sense that it uses historical data to reduce variance of the treatment response estimates (and thus reduce the minimum sample size required to achieve the desired level of confidence) better than other available approaches.**

Prognostic Covariate Adjustment (PROCOVA™) is a statistical methodology intended to improve the efficiency of Phase 2 and 3 clinical trials, by using trial subjects' predicted outcomes on placebo (prognostic scores) in linear covariate adjustment.

The intention is to confirm and further inform the **different measurement properties** of the SV95C, and to support its use as a **primary endpoint** to assess new drug efficacy in clinical trials from Phase 1 to Phase 4 for the measurement of the maximal stride velocity of patients with DMD.

Stride velocity 95th centile **measured by a valid and suitable wearable device** is intended for a context of use as **secondary endpoint** in studies in Progressive Neuro Muscular Diseases characterized by proximal muscle weakness.

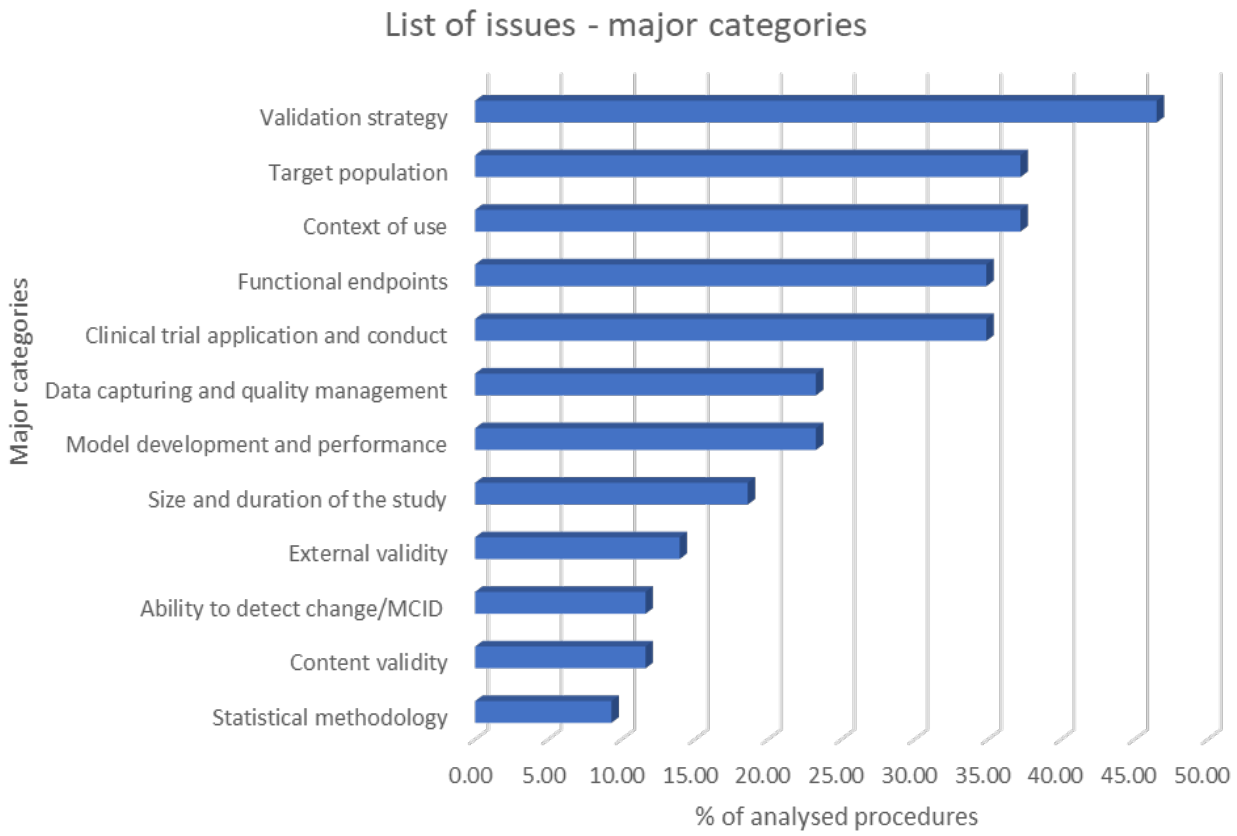
The proposed framework provides a structure that can be used to specify research questions and can inform patient preference study design, conduct, analysis and reporting when proposing undertaking patient preference studies that may inform decision-making by industry, regulators, HTA bodies and payers.

**1.** Inform on key considerations when designing, conducting and applying the results of a fit-for-purpose patient preference study (PPS);

**2.** Support regulatory decision-making when assessing and using preference study results;

**3.** Support the discussion between industry and regulators about preference studies.

# List of issues




## Examples:

**Validation strategy:**
- Anchoring to current (Gold) standard measure for intended application, or other, e.g., distribution based
- Including learn and confirm in separate datasets vs. cross-validation in pre-specified sections of one overall database

**Target population:**
- Inappropriate inclusion/exclusion criteria
- Poor representation of relevant subgroups (e.g., age, gender, ethnicity)
- Inadequate consideration of comorbidities or other relevant factors that may affect treatment outcomes

**Context of use:**
- Insufficient justification of the intended use and scope of the method
- Unclear definition or description of the target population or disease condition

**Functional endpoints:**
- Inappropriate or non-validated endpoints
- Lack of sensitivity or specificity in detecting treatment effects

**Clinical trial application and conduct:**
- Inadequate sample size or power calculation
- Incomplete reporting of adverse events
- Protocol deviations or non-compliance

# Method and technology categories analysed 2021/2022

QoNM Advices and Opinions (n=43) into main categories:

New Clinical Outcome Assessments

New Digital Tools and Imaging Methodologies

New Biomarker Qualification

New Statistical Methodologies

New methods for the development of Advanced Therapy Medicinal Products

Review > Clin Pharmacol Ther. 2022 Jul;112(1):69-80. doi: 10.1002/cpt.2554. Epub 2022 Mar 5.

# Biomarker Qualification at the European Medicines Agency: A Review of Biomarker Qualification Procedures From 2008 to 2020

Elisabeth Bakker [1], Natalie M Hendrikse [2], Falk Ehmann [2], Daniëlla S van der Meer [1 3], Jordi Llinares Garcia [2], Thorsten Vetter [2], Viktoriia Starokozhko [1 3], Peter G M Mol [1 3 4]

Affiliations + expand

PMID: 35137949 PMCID: PMC9313861 DOI: 10.1002/cpt.2554

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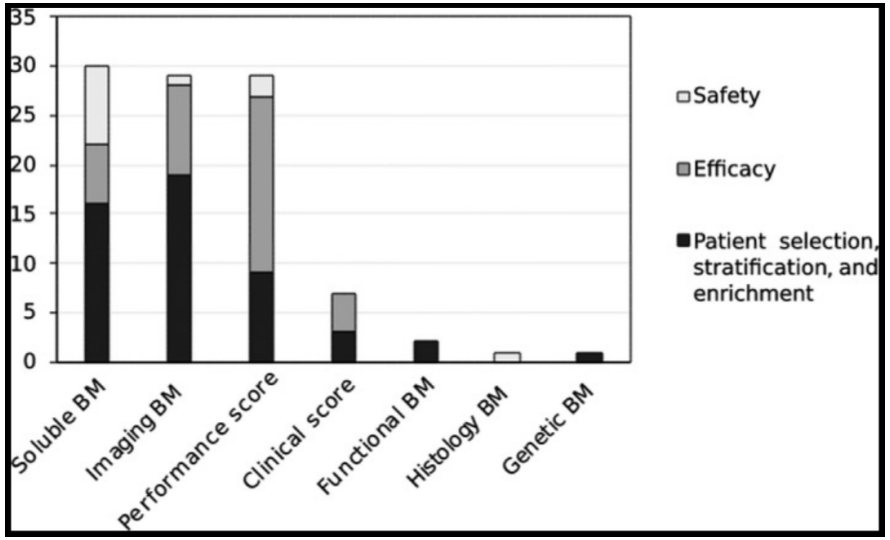


Different types of biomarkers in each CoU category. The stacked bars show the number of procedures in the three CoU categories for each type. BM, biomarker; CoU, context of use.

> Front Med (Lausanne). 2022 Apr 26;9:878942. doi: 10.3389/fmed.2022.878942. eCollection 2022.

# Biomarkers in Medicines Development–From Discovery to Regulatory Qualification and Beyond

Natalie M Hendrikse [1], Jordi Llinares Garcia [1], Thorsten Vetter [2], Anthony J Humphreys [1], Falk Ehmann [1]

Affiliations + expand

PMID: 35559349 PMCID: PMC9086587 DOI: 10.3389/fmed.2022.878942

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**Supplementary Table 2: ITF meetings with follow up in form of Scientific Advice (SA) or Qualification Advice (QA).**

| ITF meeting | Description | Follow-up |
|---|---|---|
| March 2010 | Exploratory-phase qualification of clinical Drug-Induced Liver Injury (DILI) biomarkers (safety, monitoring, diagnostic, prognostic) | QA (2013), FU-QA (2013) |
| June 2010 | General discussion on PD/Response biomarkers for clinical trials CNTO136 programme in Rheumatoid Arthritis. | SA: 3 hits, but no mention of the biomarker |
| June 2010 | Exploratory-phase qualification of clinical Drug-Induced Kidney Injury (DIKI) biomarkers (safety, monitoring, diagnostic, prognostic) | QA (2013), FU-QA (2013), FU-QA (2014), FU-QA (2016) |
| October 2010 | Exploratory-phase qualification of clinical Drug-Induced Vascular Injury (DIVI) biomarkers (safety, monitoring) | QA (2013), FU-QA (2016) |
| March 2011 | Periostin as predictive biomarker to identify patients with severe asthma that may benefit from blockade of IL13 by Lebrikizumab | QA (2012), SA (2015) |
| March 2011 | Predictive biomarker for selection of patients with "Met-positive" non-small cell lung cancer for trials | SA (2011), SA (2012) |
| September 2012 | General discussion on predictive biomarkers for clinical trials in MS | SA (2012) |
| September 2012 | Classification of cystic fibrosis patients by predictive biomarker CTFR mutations/molecular phenotypes | SA (2017) |
| December 2012 | Lung Clearance Index as a surrogate endpoint in cystic fibrosis trials | AS (2017) |
| October 2014 | General discussion on biomarkers for clinical trials in type 1 diabetes | QA (2019): not on biomarkers, but on trial protocol design |
| October 2015 | Genomic Allergen Rapid Detection (GARD): predictive biomarker signature as screening tool in early drug discovery | Applied for QOQA in December 2015, withdrawn |
| October 2018 | Biomarkers for non-alcoholic fatty liver disease and non-alcoholic steatohepatitis (Diagnostic, Prognostic, Monitoring, PD/Response) | QA (2019), QA (2019) |

# Analysing the journey of innovation:

assumption → Patents → Publications → Clinical trials → QoNM

| Context of use | Patents | CT | PubMed |
|---|---|---|---|
| **New Statistical Methodologies** | | | |
| PASS based on secondary use of data | 0 | 0 | 2 |
| Data source and infrastructure support for registry-based studies for HD | 5 | 8 | 110 |
| Self-reported questionnaire to assess anhedonia | 0 | 5 | 11 |
| Risk and response score in diabetic patients with chronic kidney disease | 21 | 11 | 187 |
| Validated tool to measure BCVA in future CTs | 0 | 6 | 463 |
| Collecting data for SMA, evaluation of safety and efficacy | 0 | 0 | 2 |
| Improve the efficiency of phase 2 & 3 CT by using prognostic scores | 0 | 0 | 3 |
| Investigating interventions to treat paediatric ulcerative colitis (UC) | 0 | 1 | 1 |
| Inform and support regulatory decision making - IMI | 2 | 1 | 14 |
| Assessment of vaso-occlusive crises reduction and morbidity in SCD | 0 | 2 | 29 |
| Evaluate the safety and efficacy of priority novel agents in B-NHL | 0 | 0 | 3459 |
| | 28 | 34 | 4281 |

Patent search results – patents found not related to the novel technology and its context of use
Clinical search results – clinical trials – 1 relevant study – Recruiting status – in line with the approved context of use
Publication search results – multiple relevant scientific papers published

# Analysing the journey of innovation:

assumption → Patents → Publications → Clinical trials → QoNM

| Context of use | Patents | CT | PubMed |
|---|---|---|---|
| **New Clinical Outcome Assessments** | | | |
| Novel clinical endpoints for CT in iAMD patients | 0 | 1 | 11 |
| Novel endpoints in iAMD clinical trials | 5 | 4 | 7 |
| Novel endpoints to asess the efficacy of therapy for AD | 0 | 1 | 0 |
| PASDAS and MDA as primary outcome intruments in PA | 11 | 19 | 22 |
| AQPA endpoint for chronic heart failure | 0 | 7 | 7 |
| Secondary endpoint in studies on Progressive Neuro Muscular Diseases | 0 | 5 | 5 |
| Assess change in symptoms and impacts over time in PwPAH | 0 | 19 | 12 |
| Surrogat endpoint the five-year risk of death-censored allograft loss | 1 | 0 | 1 |
| Human anti-IL1alpha monoclonal antibody for severe AD in adults | 0 | 1 | 0 |
| Replacement of therapeutic equivalence studies for the same active subst. | 0 | 0 | 1 |
| Acceptability testing for oral/buccal medicines in children <12 | 0 | 0 | 1 |
| Model disease progression and aid clinical trials DMD | 0 | 0 | 1 |
| IMPs to improve preservation of β cell function in T1D | 1 | 0 | 1 |
| Study the transition from auto-antibody positivity to diagnosis of T1D | 0 | 3 | 35 |
| STAR to assess treatment efficacy in pSS | 0 | 2 | 1 |
| | 18 | 62 | 105 |

Patent search results – 1 relevant patent found

Clinical search results – clinical trials – 1 relevant cohort study

Publication search results – 1 relevant scientific paper

1. >

☆ **WO2020188118A1** METHOD OF PREDICTING WHETHER A KIDNEY TRANSPLANT RECIPIENT IS AT RISK OF HAVING ALLOGRAFT LOSS

Available in ⌄ Patent Translate ⌄ ⋮

Bibliographic data | Description | Claims | Drawings | Original document | Citations | Legal events | Patent family

Published as **CN114402394A; EP3712898A1; EP3942563A1; US2022293274A1;** WO2020188118A1

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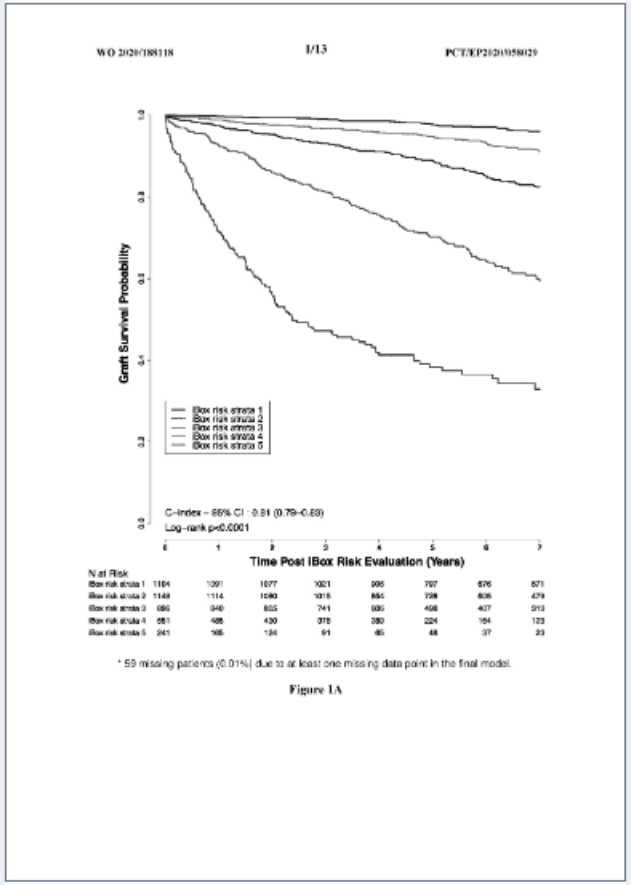
## METHOD OF PREDICTING WHETHER A KIDNEY TRANSPLANT RECIPIENT IS AT RISK OF HAVING ALLOGRAFT LOSS

### Abstract

Organ transplantation is currently recognised as the treatment of choice for patients with end-stage renal disease (ESRD), which is an underestimated but increasing burden worldwide. Despite the pressing need for improving patients risk stratification raised by transplant societies as well as regulatory agencies, no risk-stratification system exists that adequately predicts transplant patients' individual risk of allograft loss. This currently represents a limitation for improving patient management, as well as for defining early surrogate end points for clinical trials and development of pharmaceutical agents. The inventors now report the development and validation of an integrative risk prediction score to predict kidney allograft survival of individual patients (NCT03474003). The iBox risk prediction score is the first integrative system validated in several independent populations from Europe & North America as well as across 3 clinical trials (NCT01079143, Eudra CT2007-003213-13, NCT01873157) covering distinct clinical scenarios. In particular, the advantages brought by the iBox risk prediction score are i) improved discrimination performance by combining traditional prognostic factors with mechanistically informed parameters, ii) outperformance when compared with currently existing scoring systems, iii) generalisability when assessed in geographically distinct cohorts from Europe and North America, iv) transportability at different times of evaluation post-transplant, v) performance in a variety of clinical scenarios including clinical trials and vi) readily accessible to clinicians and patients by an online tool for patient risk calculation. Thus, the present invention relates to a method of predicting whether a kidney transplant recipient is at risk of having allograft loss by implementing the iBox risk prediction score.




[Espacenet – search results]

# Conclusion

- Applicants of QoNM benefit from well-defined and considered Context of Use ensuring the evidence provided supported the claim.
- The analysis of most frequent ***List of Issues*** shall guide future applicants to optimize their submission package enabling an efficient Qualification procedure.
- To effectively evaluate the journey of innovation additional analysis covering longer observation periods or combining existing data sets e.g. Biomarkers would be of value.

# Thank you for your attention!