

Collaboration, innovation, and transformation: an end-to-end approach for direct-to-patient clinical studies

A case study on METNA RA – a cross-sectional electronic survey to validate a new methotrexate treatment adherence tool in rheumatoid arthritis, in collaboration with F. Hoffmann-La Roche global medical affairs.

Pharmaceutical companies are increasingly conducting direct-to-patient clinical studies to generate endpoint data that helps prove the efficacy of investigative medical products or procedures. To achieve this, many are developing electronic patient-reported outcomes (ePRO) tools to measure aspects such as a patient's subjective quality of life or self-assessed disease severity. However, for these endpoints to be accepted by regulators, clinicians and researchers as having scientific value, ePROs must first be validated to prove they measure their intended outcomes accurately.

Validation studies can be difficult to undertake. Complexities surrounding questionnaire design and regulatory compliance are often compounded by operational challenges that can encumber patient recruitment and delay progress. Technology has helped unlock efficiencies, but the multiplicity of stakeholders and datasets in many patient studies means that most digital platforms struggle to connect processes from end-to-end – i.e., from protocol to patient. The most effective direct-to-patient studies depend on high quality data, ethical access to patient cohorts, trusted collaboration between stakeholders and efficient communication to knit everything together.

A great example is METNA RA – a psychometric validation study led by Roche global medical affairs in rheumatoid arthritis (RA). The multi-centre study was conducted in collaboration with the clinical trial technology provider **eClinicalHealth**, in collaboration with **OPEN Health** – experts in analysis of real-world data, and partners with healthcare providers across primary and secondary care; and **Optimum Patient Care (OPC)** – providers of quality improvement programmes and experts in delivery of real-world/pragmatic research in primary care. METNA RA was facilitated by **Clinpal**, eClinicalHealth's end-to-end clinical research platform, purpose-built for virtual, hybrid and direct-to-patient studies. In combination, the multi-partner approach powered impressive study recruitment and completion rates.

METNA RA Study

In 2017, Roche wanted to validate a PRO tool it had developed to assess medication adherence in rheumatoid arthritis patients being treated with Methotrexate (MTX). The tool – the MTX Experience Questionnaire (MEQ) aimed to help doctors better understand patients' experiences and identify common drivers of non-adherence. The goal was to give clinicians an instrument that would not only allow them to monitor adherence in routine clinical care, but also help them detect and manage patients with poor adherence to their MTX treatment.

METNA-RA was a multi-centre, cross-sectional, electronic survey to validate the MEQ. eClinicalHealth partnered with OPEN Health and OPC to deliver the study, maximising the **OPC Research Database (OPCRD)** and OPC's proven ability to engage, recruit and support practices to conduct clinical studies. The entire study was conducted with eClinicalHealth's state-of-the-art **Clinpal** platform – from patient enrolment to patient and physician survey completion.

Study protocol and methodology

The objective was to have >300 patients with RA completing the study within an 11-month timeframe. However, to avoid 'over-recruitment', the inclusion process would be curtailed as soon as the target number of study assessments had been completed. To achieve statistically significant results, the sample needed to include a stratified mix of adherent (70%) and non-adherent (30%) patients. This was one of the biggest challenges to the recruitment process, reinforcing the need for a robust patient database and collaboration with primary care practices to identify, enrol and engage target patients – provided by OPC.

Once enrolled, patients completed the MEQ and two generic compliance questionnaires to self-reported adherence, including a range of socio-demographic questions. Physicians (GPs) of the participants also completed an additional questionnaire related to the patient, along with a subjective assessment of their adherence to MTX using a 5-point Likert scale. These responses were then combined with a proportion of days covered (PDC) calculation – a measurement of medication adherence using retrospective prescription data over a 6 and 12-month period from the OPCRD to assess adherence using subjective and objective data as a benchmark against which to compare the MEQ responses

"The study encountered many of the familiar challenges associated with direct-to-patient research," says Karl Landert, CEO, eClinicalHealth. "These include satisfying strict privacy, security and confidentiality requirements put in place by the HRA and ethics committees; handling diverse datasets and multiple stakeholder groups; and managing workflow throughout the journey to meet defined timelines. The 'human' challenges of securing patient participation through to completion adds further layers of complexity. To achieve our goal efficiently – onboarding as few 'high density' practices as possible based on the feasibility assessment, we needed a seamless, flexible, and personalised direct-to-patient invitation process, and telephone follow-up (supported by dedicated OPC Research Coordinators) to help practices motivate patients to enrol and complete their questionnaires. This was all supported by the Clinpal platform. Our success highlights the importance of seamless collaboration between specialist partners and great technology to facilitate studies from end-to-end."

Partnerships and process

To initiate METNA RA, eClinicalHealth partnered with OPEN Health to determine the feasibility of the study, develop study design, and protocol, and establish an infrastructure for implementation. Critical requirements included finding a primary care database (OPCRD) to map the patient population, and a delivery partner (OPC) to recruit and support 'high density' practices (i.e., those with the highest numbers of eligible patients) to deliver the study. OPEN Health's experience in working with real-world data, along with its reach into the primary and secondary care ecosystem, proved crucial in identifying the datasets that would be best suited to METNA RA. It also conducted the initial PDC calculation to provide a baseline measure for the study and inform the potential stratification in the population at large, in turn informing the recruitment planning.

"The feasibility study depended on mining a primary care database to identify how many patients met the inclusion/exclusion criteria and determine the optimal route to our recruitment goal," says Chris Hodgson, Commercial Director, Europe OPEN Health "The original feasibility study estimated that to hit the target of 300 completed patient questionnaires, we would need to invite around 1000 patients. To achieve this efficiently, we needed to target high density practices – with the expectation that the sample would be drawn from 40-55 GP surgeries. The feasibility exercise was pivotal, helping to shape both the protocol design and methodology. Through that collaborative process – leveraging our partner network and drawing on expertise in evaluating real world datasets – we identified OPC as our delivery partner. This allowed us to build on our existing relationship with OPC and maximise its acclaimed research database (OPCRD)."

The partnership with OPC – a social enterprise that works with general practices to carry out quality improvement programmes and ethically approved research, strengthened METNA RA's reach into primary care. It allowed the study to leverage OPC's relationship and access to over 800 practices in the UK. It also provided access to OPCRd – a longitudinal electronic medical record (EMR) database of 13 million patients, with fully characterised chronic disease data.

"Our role was to identify and recruit appropriate GP surgeries and provide all the support they needed to invite and enrol eligible patients with personalised phone support," says Francis Appiagyei, Clinical Manager, OPC. "We worked closely with practices to minimise the administrative/operational burden of the study and ensure participants completed the online questionnaire. We provided telephone support for patients that didn't have access to internet or had limited computer literacy. Finally, we used OPCRd to collect the patient data required from practices for PDC calculation and study analysis. This information was combined with all other data captured through Clinpal, to form the full study dataset for analysis."

End-to-end delivery

The end-to-end process – from identifying high density practices and eligible patients, to recruiting, inviting, and engaging participants, through to questionnaire completion – was facilitated by the Clinpal platform.

"Practices that signed up to the study were equipped with Clinpal," says Karl Landert. "To help them, we loaded the platform with anonymised data and a 'key' from OPCRd – so practices accessing the system could de-anonymize eligible patients and automatically invite them to join the study via an automated mailing on practice-branded letterheads. A reward voucher was offered to incentivize participation."

"Patients signed up online using an activation code, which provided access to an explainer video. Enrolment involved a stringent online 'Consent' process built into Clinpal. Upon giving consent, participants completed the online questionnaires which, in turn, triggered the practices to complete their own patient-related charts and questionnaires. Clinpal's workflow automation, strengthened by OPC Coordinators, who provided support for participating surgeries – minimised the burden on practices, allowed us to build a deep study dataset that combined information from three distinct sources."

The use of integrated technology was fundamental to METNA RA's success. Clinpal contributed at every touchpoint of the direct-to-patient study, in particular:

- Engaging and educating GP practices and patients via a secure web portal
- Inviting and recruiting pre-qualified patients into the study
- Managing eConsent
- Capturing information through patient and physician questionnaires
- Supporting workflow, such as automated reminders/notifications, personalised dashboards, reward system management
- Merging the patient questionnaire data, the clinician reported data and the EMR prescription data into one system at patient completion – providing a complete analysis dataset

The result

METNA RA study enrolled 325 patients, with 320 successfully completing questionnaires. The targeted stratified mix was achieved, with 228 adherent (71%) and 92 non-adherent (29%) patients completing the study. Overall, the study invited 1,043 patients across 51 practices. The enrolment and completion rates of circa 31% exceed industry standards for direct-to-patient studies. The final study dataset was drawn from 38 practices, in line with original estimates. Results from this study have been recently published by Curtis et al, concluding that the 24-item MEQ is a reliable and valid instrument to assess the adherence of RA patients taking MTX and that this information should facilitate clinician-patient discussions and help inform treatment decisions.

66 The results are, first and foremost, a testament to the collaboration between our expert partners, **OPEN Health** provided invaluable insight that helped shape the feasibility study and protocol design – and they were the conduit to the primary and secondary care data and relationships that drove the study. **OPC**'s access to and trusted relationships with primary care providers and support model with Research Coordinators, was instrumental in the study's success. Alongside it, **Clinpal** provided a digital engine that helped connect stakeholders, automate processes, manage workflow efficiently and collect study data. As METNA RA shows, end-to-end platforms can transform processes and bring operational efficiencies to complex direct-to-patient studies. When combined with specialist partners working in true collaboration, the potential to improve outcomes is significant.

Karl Landert, CEO, eClinicalHealth.

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Reference

1. Curtis, J.R., Nebesky, J.M., de Bock, E. et al. Development and validation of the Methotrexate Experience Questionnaire, a new methotrexate oral treatment adherence tool in rheumatoid arthritis. *J Patient Rep Outcomes* 5, 69 (2021). <https://doi.org/10.1186/s41687-021-00339-5>.