Final project report

Applied Public-Private Research enabling OsteoArthritis Clinical Headway

APPROACH

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1. Executive summary

1.1. Project rationale and overall objectives of the project

It has been suggested that 10% of men and 18% of women above 60 suffer from osteoarthritis (OA), and a quarter of those affected struggle to carry out ordinary daily activities. Despite the large and growing burden of this disease, many pharmaceutical companies have reduced or altogether abandoned drug development. One of the problems is that there are currently no reliable ways of measuring whether a specific treatment is working or not. This is partly because the mechanisms that lead to the disease in different subgroups of patients, are poorly understood. Moreover, although the current mind-set for treatment in this field is moving towards personalised medicine, there are no accepted methods of classifying the patients according to diagnosis methodology, prognosis and treatment plan.

The APPROACH consortium used a combination of biomedical data for more than 10,000 OA patients and heathy people from 8 existing cohorts into a unified bioinformatics platform with the aim of identifying different OA phenotypes. These phenotypes were then be validated in a longitudinal cohort using existing and newly-developed biomarkers. This enables the development of guidelines for differentially diagnosing the right patient for the right treatment.

The project ran for 6.5 years, from June 2015 to November 2021. The overall objectives of the consortium were:

- Implement and establish a new, integrated and comprehensive database platform of existing data from partners that will be extended with newly collected longitudinal data, incorporating novel high-quality biomarkers.
- Define subsets of (phenotypically) different patients in the existing cohorts and refine these in the successive new longitudinal extension cohort and subsequently identify the "right patient" to treat for each subset/phenotype via innovative stratification techniques.
- Optimise, introduce and validate the next generation imaging methodologies (modality + post-processing), human motion analysis and biochemical assays to enable more efficient and reliable diagnoses and treatment of OA patients, refining stratification of phenotypes.
- Identify mechanistic targets for patient subsets, create prediction models and establish guidelines for a disease modifying osteoarthritis drug (DMOAD) development that forms the roadmap for OA.

1.2. Overall deliverables of the project

At the end of the project, APPROACH was expected to provide the following tools, methods and definitions that can be used to optimise future clinical trials for OA:

- An integrated bioinformatics platform that functions as a repository of clinical data, biomarker data, images, as well as storage of bio-samples from a broad spectrum of OA patients. End of project outcome: This was delivered with the consolidation of the APPROACH clinical study and historical public OA patient data into the database located at the Digital Research Environment (DRE), which acts as an accessible data repository with integrated bioinformatic platform for the consortium. Public interface with APPROACH can be accessed via FAIRplus (Elixir). A description of the integration of APPROACH data into FAIRplus is highlighted in this FAIRplus case study report.
- A set of well-defined subsets of OA patients with existing and novel marker acquisitions in an on-going longitudinal cohort enabling bioinformatics to stratify the patients in

targetable subsets and - if needed – to derive very early markers using the oldest data in the repository established in D1. End of project outcome: This was delivered with the publication of Angelini, et al. 2022. http://dx.doi.org/10.1136/annrheumdis-2021-221763

- Clinically applicable next generation markers based on imaging, locomotion and biochemical/omics methods. End of project outcome: This was delivered with the completion of the clinical study portion of the project with all data acquired and numerous publications describing the results. A list of relevant publications with links to full text access can be found on the APPROACH website.
- Validation and qualification of diagnostic methods and criteria that are well described in guidelines and used in prediction models to support new DMOAD trials, with medication that is specifically designed for subsets of phenotypically different OA patients. End of project outcome: This was partially completed by the end of the project and is an intended focus of the consensus report and future analysis and publications to further exploit the findings of the consortium.

Finally, APPROACH is expected to deliver a comprehensive consensus report describing how to stratify OA patients in phenotypes that can be targeted with putative DMOAD therapies in subset dependent trial protocols. This will support the regulatory bodies, such as European Medicines Agency (EMA), to direct and apply guidelines for the use of defined, validated and specific endpoints in OA clinical trials. End of project outcome: This was not completed by the end of the project but is an intended focus of the close-out meeting to be held in 2022. In addition. It will be published in the future.

1.3. Summary of progress versus plan since last period

The APPROACH project formally started in June 2015. The main effort of the first four reporting periods was to set up the project, secure local ethical and institutional clinical protocol approval, and initiate enrolment and complete follow-up visits of the longitudinal cohort (the 'APPROACH study') at five clinical centres across Europe and start the analysis of patient samples. Although project activities were significantly impacted by the global pandemic during the fifth reporting period, the consortium partners were able to quickly adapt to the changing and increasingly restrictive landscape to minimise the negative impact on patient visits and focus on sample analysis to deliver data.

Although still impacted by the global pandemic, the sixth reporting period observed full completion of required patient visits (24-month timepoint) by April 2021 at all of the clinical centres. The clinical eCRF management responsibilities were completed by July 2021 to effectively close the in-life portion of the APPROACH cohort study. Dissemination of data into the database and patient samples for analysis, testing and storage was completed by July 2021. Initial analysis of the clinical data officially commenced in August 2021 and delivery of the majority of the data from clinical patient sample analysis was complete by September 2021. A few additional sample analysis activities included and approved in Amendment 6 (e.g., metabolomics) were started later in 2021, but have now been completed with upload of the data taking place in Feb 2022. Therefore, although data from some additional analyses may still be added over time to enhance the dataset, the major goals of completing the clinical study, data generation from clinical samples and images and delivery of the APPROACH cohort database is essentially complete as of this final report.

The only exceptions to this are a few deliverables, one milestone and the final consensus report. Specifically:

1. The whole body CT reading deliverable for the final timepoint (month 24) was not completed prior to the end of the project due to resourcing issues. However, this analysis is ongoing and will be completed post-project using independent funding and included in the database for future public access via FAIRplus.
2. MRI-based 3D cartilage surface, joint space and cortical bone mapping deliverable was not completed in full prior to the end of the project due to resourcing issues. However, this analysis is ongoing and will be completed post-project using independent funding and included in the database for future public access via FAIRplus.
3. The omics-based identification and verification of novel OA biomarkers milestone was not completed in full prior to the end of the project due to the need for additional analysis and follow up validation. This activity is ongoing and, because it is a discovery-based outcome, is not critical for completion of the database. It is anticipated that results of this activity will be the subject of future publications from the consortium.
4. The final consensus report deliverable was not completed in full prior to the end of the project due to the need for a more in-depth analysis of the data to be completed. Although there have been a number of published findings coming from the consortium that provide a strong foundation for the objectives of the project, the consensus report would benefit from additional analysis in order to provide a more thorough perspective and recommendations. This report will be the focus of post-project activities and in preparation for the close-out meeting with the IMI review board. The final consensus report will be completed post-project using independent funding and ultimately submitted for publication.

Critical to overall project goals, analysis of the data generated from the clinical phase of the project has begun in earnest during this last period. Significant collaboration across work packages 1-3 has led, not only, to delivery of planned analysis outputs, as exemplified by work involving identification and characterisation of biomarker-based patient subsets (see section 2.5.1) and numerous publications, focused on clinical study results and characterisation of different endpoints employed in the study (see section 3.2), but also initiation of novel analytical strategies that have arisen since the inception of the project. Although we are starting to get useful results which we plan to present in more detail during the IMI project close out meeting later this year, this work is still in its early stages and the consortium is confident that the APPROACH data set will continue to provide a valuable source for future analysis, publications, funding opportunities and therapeutic clinical trial design application for many years to come. Furthermore, the foundational rationale, strategies and techniques conceived and applied in this effort have created a strong precedent for addressing fundamental challenges associated with complex diseases like osteoarthritis.

Notably, although many in-person activities were curtailed during the pandemic period, the consortium partners continued to focus on strategy, deliverables and publication outputs to meet project goals. Importantly, the consortium was able to hold a very successful hybrid in-person/virtual final meeting in Zeist, NL in November 2021, with approximately 70% of the consortium membership attending in person. This was a very enjoyable and productive gathering of the membership, especially considering nearly 2 years had elapsed since the previous face-to-face meeting in A Coruna, Spain in 2019. Beyond the robust scientific and medical discussions, the spirit of the meeting, and consortium as a whole, was exemplified by a rousing presentation from the APPROACH patient council members. Their dedication to the consortium over the course of the project, delivery of a unique publication on their role in the project (see section 3.2) and heartfelt guidance on behalf of the APPROACH cohort participants offers a refreshing reminder of the value of this type of project for patients in need.

1.4. Significant achievements since last report

1.4.1. Bioinformatics (WP1): Implementation of a machine learning model for patient enrolment and management of the APPROACH databases.

During the 6th reporting period WP1 activities focused on initial assessments of the results generated in the APPROACH clinical cohort with regard to predictive power of the clinical screening/enrolment algorithms on pain and structural progression phenotypes as well as identification of patient subsets based on biochemical signatures at the baseline timepoint (see section 2.5.1 and Angelini, et al. for more detail).

- Continuous management of database systems for central data storage has been ensured with transfer of database to the DRE (to be managed by UMCU) – completed in 4Q2021.
- Two manuscripts, facilitated by WP1 in collaboration with WP2 and 3, have been accepted/submitted for publication during this reporting period.

1.4.2. Biochemical markers and omics (WP2): Enabling APPROACH study sample testing

During the 6th reporting period, WP2 has been very active in the distribution and testing of clinical samples to meet project timelines. This included significant logistics for collection of thousands of clinical samples from the 5 clinical sites and distribution to testing/storage facilities and generation of various biochemical and -omic data endpoints at 10 testing facilities spanning 8 partner sites.

- Sample logistics
    - GSK: Coordinated the distribution of over 30,000 APPROACH clinical samples to their final destinations for testing or storage which was completed by end of 2Q2021.
        - Long-term storage of remaining serum samples will be maintained at a contracted facility in Germany by GSK on behalf of the consortium.
        - Remaining isolated RNA and DNA samples from respective transcriptomic and methylomic/genomic analysis were distributed to, or retained at, Newcastle for storage and potential future analysis.
        - In accordance with the informed consents, all remaining APPROACH samples will be maintained for a maximum of 15 years from clinical study completion (April 2021) or when exhausted, whichever comes first.
        - Subsequent management decisions on distribution, testing and fate of these samples will be governed by the APPROACH sustainability steering committee (including the 5 clinical site PI's) going forward.
- Biochemical markers
    - Nordic: Successful delivery of data on 15 markers from serum and/or urine (C3M, CRPM, CTX-I, HA, hsCRP, PRO-C2, huARGS, NMID, COMP, urine CTX-II, alphaCTX-I, C2M, urine CREA, reC1M, and C10C) across all timepoints completed in 3Q2021. QC and initial analysis completed for data upload in 4Q2021.
    - Artialis: Successful delivery of data on serum Coll2-1 and Coll2-1NO2 across all timepoints completed in 3Q2021 with QC and initial analysis for data upload in 4Q2021.
    - Lund: Successful delivery of data on serum ARGS neoepitope biomarker across all timepoints completed in 3Q2021 with QC and initial analysis for data upload in 4Q2021.

- Oulu: Successful delivery of serum data on a multiplex panel of 24 inflammation-based analytes across all timepoints completed in 4Q2021 with QC and initial analysis for data upload by 2Q2022.

- Omics
  - Lipidomics (LUMC): Delivery of lipidomic data (baseline) was completed in 2020 with upload of data. In-depth analysis of the data was undertaken during 2021 resulting in the submission of a foundational manuscript on the findings (see Kloppenburg et al. in dissemination section).
  - Proteomics (Sergas and Lund): Successful delivery of proteomic data from baseline samples for data upload was completed in 3Q2021. QC and initial analysis completed in 4Q2021.
  - Transcriptomics (Servier): Successful delivery of RNAseq data from both baseline and M024 visits was completed 3Q2021 with QC and initial analysis completed for data upload in 4Q2021.
  - Methylomics (Newcastle): Successful delivery of data from baseline and M024 visits achieved for data upload in 4Q2021.
  - Genomics (Newcastle): Successful delivery of genotyping data (Baseline visit only) was achieved in 3Q2021 with QC and initial analysis completed for data upload in 4Q2021.
  - Metabolomics (Oulu): Successfully contracted and distributed samples to a sub-contractor (Nightingale) for metabolomic testing in advance of the project end date (30 Nov 2021) for data delivery in 1Q2022. Final data was successfully delivered in Jan 2022 to be uploaded into the APPROACH database.
- WP2 partners have been actively publishing foreground and sideground manuscripts relevant to the APPROACH project (see dissemination section). This is expected to continue as wider analysis within datasets and across the breadth of APPROACH data takes place, especially in collaboration with WP1 and 3 colleagues.

1.4.3. The APPROACH study: the clinical cohort (WP3)

WP3 has put a large amount of effort this period into clinical cohort management in order to ensure completion of the final M24 visits of the APPROACH cohort and complete necessary documentation to finalise the study and conclude eCRF-related activities. This was necessary, not only from an active clinical monitoring perspective, but also to allow sufficient time for image and sample distribution and analysis to take place for delivery of data prior to project completion. Although some of the M24 visit timing needed to be adjusted to accommodate pandemic-related restrictions, all visits were completed by April 2021 and only a modest number (~6%) of final visits were impacted with a skew of -02 to +04 months. Although not optimal, this adjustment was necessary and is not anticipated to impose a significant challenge on data analysis.

- The APPROACH clinical study has successfully completed with ~83% (247/297) of participants completing the full two-year study duration. *Note for context: a 17% loss to follow-up rate over a 24-month timeframe is not abnormal in clinical practice and the clinical center staff and participants are to be commended for their efforts and overall dedication to the study, especially considering the pandemic-associated challenges encountered over the final year.*
- Servier delivered a thorough process of data review and cleaning prior to closure of the eCRF by the end of 2Q2021.

- The longitudinal evaluation of MRIs (3D surface mapping pending), radiographs, CTs (apart from M024 timepoint), hand scans and gait analysis have been completed by numerous partners and sub-contractors during this reporting period with data uploaded into the APPROACH database between 3-4Q2021.
- First analyses have been performed and resulted in publications and abstracts to be presented at scientific meetings (see dissemination section).
    - The primary goal to improve selection of progressive patients was successful, specifically for pain and to a lesser extent for structural damage progression (van Helvoort et al).
    - The extremely rich APPROACH dataset provides data at multiple platforms from clinical, imaging, biochemical to functional parameters and will enable further improvement of the algorithms to identify progressive patients. Moreover, it will enable identifying specific clinical phenotypes (such as a neuropathic pain phenotype; van Helvoort et al).
    - The consortium members will use the data to develop more robust and sensitive tools to evaluate the efficacy of future treatments specifically for specific characteristics of the disease. Additionally, they will develop more targeted (personalised) tools for the identification of patients with specific pheno/endo- types of OA to include in clinical trials (not restricted to drugs) development (as exemplified by Angelini, et al).

1.4.4. Internal and external communication (WP4):

- Bi-annual editions of the Participant Newsletters and Consortium Newsletters were released
- The APPROACH Twitter profile has received frequent updates and gained a larger audience.
- The website has been frequently updated with news stories and publications.
- In November 2021 we held the APPROACH Final Consortium meeting as a hybrid event in Zeist, the Netherlands

1.4.5. Dissemination of results (WP4)

- The pipeline of upcoming APPROACH scientific publications is continuously monitored with our "Publication Plan'" and ongoing publications are ad-hoc reviewed by the "Publication Committee".
- The online "Publication Approval System" (to control for IP opportunities) is used for all external publications and presentations that include project results.
- Four APPROACH scientific papers have been published in 2021 with 4 additional manuscript submissions taking place over the same timeframe.
- The Patient Council published a scientific paper on the topic of patient involvement in clinical research (Taylor et al.).
- In November 2021 we produced an APPROACH video series explaining the work carried out in the project, the results achieved as well as the way forward for the analysis of data. Next to this, two other videos were recorded with the Patient Council chair and members, who shared their learnings and impressions from the project.

1.4.6. Patient Engagement (WP4)

- Regular teleconferences with the Patient Council (PC) were held during the year to discuss study progress and to receive their input on newsletters, consortium disseminations, study progression and results.

- Individual PC members gave ad-hoc advice to questions from local clinical sites.
- The PC gave an interactive presentation during the Final Consortium meeting in November 2021
- The PC worked on a scientific publication on Patient Engagement, published in April 2021
- APPROACH was represented at IMI's webinar on patient involvement by Patient Council chair Jane Taylor who spoke about the learnings from involving patient advocates in the project.
- Jon Skandsen was invited to talk about patient involvement in research in the APPROACH project, at the Diakonhjemmets Hospital, Oslo.

1.4.7. Final year management and the next steps towards a sustainability plan

- The Executive Project Management Team coordinated the final execution of all project plans within the available budgets and time.
- A sustainability plan has been created that describes the future of the APPROACH project which will enable a more complete analysis of the results and assess opportunities for wider application/exploitation of the findings.
    - Future governance structure and access to data and clinical samples has been defined, in principle. However, formal contracting for partners is ongoing and expected to be finalised by June 2022. It is anticipated that this contract will encompass up to a 5-year extension, or until the consortium transitions the data to public access.
- Expanding on the foundation and data generated in the APPROACH consortium, additional opportunities for funding, such as Horizon 2020 and other EU-based grant agencies, are actively being pursued to retain momentum and enhance scientific, medical and societal value of the project.

1.5. Scientific and technical results/foregrounds of the project

1.5.1. Scientific results

Results and findings from the APPROACH consortium, as exemplified by the publications below, demonstrate the successful progress and potential exploitation of the project to benefit therapeutic development for patients living with osteoarthritis. Perhaps most indicative of this potential application of the project findings to therapeutic development to date is the recent publication from Angelini, et al. Osteoarthritis Endotype Discovery via Clustering of Biochemical Marker Data, which describes three OA patient endotypes (e.g. subsets) that can be easily detected with blood tests for clinical stratification and alignment to therapeutic interventions. These interventions are not limited to new drugs and surgical approaches and should also include non-invasive approaches such as bracing, physiotherapy, etc. The consortium foundationally believes that not all patients with osteoarthritis necessarily require a drug or surgery, and through a better understanding of the characteristics of OA patient subsets the most effective approach for the individual patient can be applied.

Publications:

- List of all consortium publications can be found on the APPROACH website: https://www.approachproject.eu/about/results-and-publications/scientific-articles
    - The final reporting period witnessed the publication of five APPROACH manuscripts (van Helvoort et al. x3, Angelini et al. and Taylor et al.) and submission of another

four (van Helvoort et al. x2, Loef et al. and Widera et al.) covering a diverse set of topics and representing a distinct acceleration in dissemination of project findings.

- List of all scientific meeting abstracts and poster presentations from the consortium can be found on the APPROACH website: https://www.approachproject.eu/about/results-and-publications/poster-presentations
    - Submission of four abstracts for the OARSI 2022 Congress (Jansen et al. X2, Maschek et al. and Roemer et al.) during the final reporting period sets the foundation for the next wave of publications.
- Press releases issued during the course of the project can be found on the APPROACH website: https://www.approachproject.eu/newsroom
- Patient engagement activities for the consortium including project newsletters and participant brochures can be found on the patient council section of the APPROACH website: https://www.approachproject.eu/patient-council

1.5.2. Technical results

- The APPROACH project has assembled the largest (>10,000) consolidated public/private longitudinal OA patient database in the research field.
- APPROACH dataset public interface can be located via FAIRplus/Elixir with a further description of the data integration process in this FAIRplus case study report.
- The APPROACH project successfully applied computational algorithms (e.g. computer-based models) to prospectively enroll and collect two-years of in-depth clinical and research data on 297 OA patients across five European clinical sites. The algorithms focus on predicting patients most likely to demonstrate pain and/or structural disease progression (the APPROACH Cohort).
- Computational algorithms developed within the APPROACH project have demonstrated the ability to identify OA patients based on a small number of clinical parameters aimed at predicting the likelihood of disease progression (e.g. prognostic models) within a two-year period. As analysis progresses in the post-project phase and the predictive power of the algorithms is assessed they will be refined and enhanced. Coupled with the prognostic models aimed at predicting disease progression, the clinical, gait, biochemical, omic and image-based analysis performed within the APPROACH cohort study, the consortium intends to further refine and improve the ability to predict outcomes and identify patient subsets.
- Code generated for automated analysis of knee x-rays to generate KIDA-like measure (UMCU). It is anticipated that this method will enhance compatibility of APPROACH data with other existing and future independent osteoarthritis cohorts whereby facilitating harmonisation and streamlining analysis across datasets.

1.6. Potential impact and main dissemination activities and exploitation of results

Benefits to the socio-economic and health of European (and worldwide) citizens is absolutely fundamental to the APPROACH consortium strategy. From the outset of the project, it was recognised that the limitations in treatment options for the millions of individuals living with osteoarthritis and the significant economic impacts on society created a huge unmet need. Coupled with the learnings from historical efforts to develop new treatments which typically relied on a 'one-size-fits all' mindset, which have largely been unsuccessful, the consortium has undertaken an

ambitious effort to better understand the OA patient population with the goal of identifying and characterising patient subsets which can be identified through routine clinical tests and measures and used to tailor specific treatments to the patients most likely to benefit from a given intervention. This is clearly still a work in progress for the consortium that will continue in the coming years, but we are beginning to see the potential of the effort to deliver on these goals, as exemplified by a series of published findings, notably the recent OA patient endotype publication from Angelini, et al. 2022 that provides a foundation for applied patient stratification.

It is our expectation that the findings from APPROACH will continue to be published in earnest over the coming years and can be used not only to aide interventional clinical trial design and non-interventional therapeutic strategies, but also to foster more collaboration and create opportunities for European-based biopharmaceutical research and development to grow.

1.7. Lessons learned and further opportunities for research

Quite frankly, the kind of broad and ambitious effort undertaken by the APPROACH consortium, to address pre-competitive insights into a complex disease like osteoarthritis and setting a foundation for future clinical trial design, would not have been possible outside of a public private partnership framework where a free flow of information and ideas was possible. Without this type of endeavour by an engaged team of experts, gaps in the ability of society to efficiently and effectively treat patients would remain, as basic/clinical research and therapeutic development would likely continue to be performed in relative isolation.

Communication – The importance of fostering and supporting a collaborative environment in the partnership, that includes diverse perspectives, cannot be understated.

Patient representation – Engage, listen to and enact advice from patients. Always remember the patients are who we are trying to reach and ultimately treat. As basic researchers and clinical scientists, the opportunity to speak directly with patients affected by the disease is not a given. Many researchers have very limited options to get a clear understanding of the patient perspective outside of reading publications and perhaps having a friend or family member with the condition. Although most of the members of the APPROACH consortium did not have direct interaction with the participants who took part in the clinical study portion of the project, the APPROACH patient council, a project-embedded group of 5-7 individuals with diagnosed osteoarthritis, was an invaluable source of guidance and dialogue over the entire course of the project. Through this interaction the researchers could gain insights into the condition, hear a patient-focused perspective and ultimately garner friendships. In return, the patient council was able to impart their perspective, shape the project strategy, engage directly with the clinical study participants and create a strong bond of friendship and trust within the council and with the consortium members.

Face-to-face opportunities – Take every and all opportunities to meet with your consortium partners face-to-face. Hold consortium meetings in parallel with conferences where partners will be in attendance to reduce travel and synergize with the conference energy and infrastructure. In our experience, we utilized the annual OARSI congress as the location where we held our annual steering committee meeting throughout the project. This allowed us to not only minimize travel budgets, but also it was possible to reserve free space in the conference centre via the congress. If not possible, locate venues in geographically central, and cost effective, locations to the consortium partners home sites to minimize cost and travel distance. In addition, and/or alternatively, utilize the existing infrastructure of the private/industry partners, who may be able to host meetings on their respective sites.

Technological opportunities and barriers - Solutions for virtual meetings and collaboration are always necessary for this type of broad geographic consortium, but these can still pose technical and organisational challenges. Technical challenges will always be present and notably the pandemic experience has ushered in improvements in the available tools. However, although we frequently looked to improve, and sought feedback from partners throughout the project, finding a viable path forward that works for all is not aways possible. Because consensus solutions need to be adopted, not all partners had the same level of interaction potential during some phases of the project. For example, due organisational rules not all partners were allowed to use the available video conferencing platforms and were frequently limited to audio only connections. This was obviously not ideal, not only for those directly affected partners, but also to the consortium as a whole. Finding the most viable communication solutions as early as possible during the consortium activities and/or finding alternative methods to foster the collaborative spirit is crucial. Email communication serves a necessary role in communication, but it has many well-described limitations and should not be relied upon solely, especially when working across a consortium with many different partner native languages and cultures.

Advice from experts – Encourage, accept and implement feedback from independent experts in the field that come through the various advisory boards who advise the project. These came to us via the Scientific Advisory Board (SAB) on the project as well as the review boards which were assembled by the IMI at the beginning, mid-way point and the end of the project. Always remember that although their advice can at times feel critical it is delivered in the best interest of a successful project outcome. Learn from it and adjust accordingly.

Sustainability planning – One may consider that when the project is complete (e.g. when funding runs out) that everyone goes their separate ways and returns to their own work. This should never be the case, unless of course everyone realizes they don't wish to work together any longer (if so, that's likely a more fundamental and problematic issue that was not experienced in this project and will not be covered here...). Rather, successful completion of a consortium should represent a 'jumping-off' point for future grants to further utilize the data and learnings and seed ongoing collaboration amongst the partners and the wider research community. In our example, we have submitted a Horizon 2020 grant application to build on the analysis and application of the data generated within the APPROACH consortium. If funded, this will ultimately represent a second wave of the consortium. That said, even if this application is not funded, the APPROACH collaboration will not stop here, as we are currently setting up an infrastructural agreement amongst the partners to continue the collaboration for an additional 5-year period. This will allow us to continue to work together to further analyse the data and work with collaborators external to the original consortium partner ranks.