Brussels, 27 May 2022

COST 061/22

DECISION

Subject: Memorandum of Understanding for the implementation of the COST Action "European Network on Optimising Treatment with Therapeutic Antibodies in chronic inflammatory diseases" (ENOTTA) CA21147

The COST Member Countries will find attached the Memorandum of Understanding for the COST Action European Network on Optimising Treatment with Therapeutic Antibodies in chronic inflammatory diseases approved by the Committee of Senior Officials through written procedure on 27 May 2022.

MEMORANDUM OF UNDERSTANDING

For the implementation of a COST Action designated as

COST Action CA21147
EUROPEAN NETWORK ON OPTIMISING TREATMENT WITH THERAPEUTIC ANTIBODIES IN CHRONIC INFLAMMATORY DISEASES (ENOTTA)

The COST Members through the present Memorandum of Understanding (MoU) wish to undertake joint activities of mutual interest and declare their common intention to participate in the COST Action, referred to above and described in the Technical Annex of this MoU.

The Action will be carried out in accordance with the set of COST Implementation Rules approved by the Committee of Senior Officials (CSO), or any document amending or replacing them.

The main aim and objective of the Action is to eliminate the barriers and raise awareness of the implementation of individualised (TDM-guided) dose optimisation of therapeutic antibodies for chronic inflammatory diseases in daily clinical practice, throughout Europe. This will be achieved through the specific objectives detailed in the Technical Annex.

The present MoU enters into force on the date of the approval of the COST Action by the CSO.

OVERVIEW

Summary
Although treatment of chronic inflammatory diseases has been revolutionised with the introduction of targeted therapies with therapeutic antibodies, a large portion of patients do not respond to treatment or they lose response over time. This is mainly attributed to suboptimal dosing, immunogenicity and interpatient variability in pharmacokinetics. To overcome the problems of suboptimal treatment, researchers have started to focus on individualised treatment optimisation strategies based on development of patient stratification tools and therapeutic drug monitoring (TDM)-guided dose adaptations based on serum drug concentrations.
A substantial improvement in patient care will be realised by implementing individualised (TDM-guided) dosing schemes of therapeutic antibodies in daily clinical practice for treatment of chronic inflammatory diseases, which will ultimately result in a more cost-effective use of these expensive drugs ("the right drug at the right dose for the right patient"). However, expertise on individualised (TDM-guided) treatment optimisation is highly fragmented in Europe, and largely limited to a few pioneering centres. Transferring knowledge and techniques to other (peripheral) centres is challenging, especially due to the need for inhouse expertise and a lack of standardisation in TDM assays. Therefore, this Action will create an interdisciplinary, pan-European Network in order to defragment and structure the scientific research in this field and to facilitate the implementation of individualised (TDM-guided) cost-effective dose optimisation of therapeutic antibodies in daily clinical practice for treatment of chronic inflammatory diseases.

Areas of Expertise Relevant for the Action	**Keywords**
● Health Sciences: Health services, health care research ● Medical engineering: Databases, data mining, data curation, computational modelling ● Clinical medicine: Rheumatology ● Clinical medicine: Gastroenterology and hepatology ● Clinical medicine: Dermatology and venereal diseases	● Inflammatory chronic diseases ● Biopharmaceuticals ● Cost-effectiveness ● Drug monitoring ● Precision medicine

Specific Objectives
To achieve the main objective described in this MoU, the following specific objectives shall be accomplished:

Research Coordination
● Create an interdisciplinary society of researchers, clinicians, experts and stakeholders in order to defragment the European research community working on dose optimisation of therapeutic antibodies.
● Investigate and develop patient stratification tools to predict and optimise treatment with therapeutic antibodies, before and upon the start of treatment, with the contribution of predictive analytic companies or academic groups.
● Develop guidelines for clinical management and best practices for individualised (TDM-guided) dose optimisation.
● Improve the reproducibility, standardisation and harmonisation of TDM assays and protocols.
● Set up a comprehensive and structured overview on the availability of patient data/samples, and the availability of TDM assays across all participating hospital/research centres.
● Evaluate the cost-effectiveness of individualised (TDM-guided) dose optimisation of therapeutic antibodies as an instrument to reduce healthcare expenditures, thus ensuring access and affordability.
● Investigate how TDM may be implemented and secured in the community with the support of e-Health

SMEs.
● Disseminate knowledge and findings within the scientific and clinical community and to policymakers.

Capacity Building
● Facilitate scientific collaboration and knowledge exchange by organising and coordinating an open, sustainable, and multidisciplinary network using an electronic platform.
● Stimulate the development of a joint research agenda to facilitate the development of new research projects, post-marketing studies and prospective multicentre clinical trials.
● Offer a balanced vision and expertise to European and national decision-makers by their participation in the network as external advisors and by targeted communication measures.
● Identify and interact with stakeholders. Stakeholders will be actively identified among Action members and their networks but also beyond.
● Form an educational programme to offer training in different multidisciplinary areas embedded in this Action, allow for dissemination of knowledge and research outputs, and open opportunities to interact with and learn from more experienced research groups.
● Help Young Researchers and researchers from inclusiveness target countries (ITCs) develop and expand their professional networks, meet experts and stakeholders, and create opportunities for collaborations.
● Support researcher mobility by encouraging Young Researchers and ITC researchers to participate in training schools and STSMs. The Action will strive for a fair and diverse membership and will promote gender equality.
● Give the opportunity to SMEs and pharmaceutical companies to join the Action (pharmacometricians, biostatisticians, assay developers, software producers, data managers and clinical trial designers).

TECHNICAL ANNEX

1 S&T EXCELLENCE

1.1 SOUNDNESS OF THE CHALLENGE

1.1.1 DESCRIPTION OF THE STATE-OF-THE-ART

Although different chronic inflammatory diseases have their unique epidemiology and pathophysiology, they are all characterised by a dysregulation of the normal immune response with an imbalance in levels of pro-inflammatory cytokines and a prolonged and variable course of remission and relapse. These diseases typically start early in life, thereby affecting the quality of life and productivity of young and active individuals. Because of no available cure, patients require life-long treatment, which requires safe, tolerable and cost-effective treatments.

Treatment with therapeutic monoclonal antibodies and antibody-related molecules, hereafter collectively called therapeutic antibodies (e.g., infliximab, adalimumab, etanercept, rituximab) usually provide a tight disease control, and optimal use of these powerful drugs can lead to improved quality of life, decreased disability and improved work/school productivity. However, the success of the therapeutic antibodies is hampered by not all patients showing favourable response to these treatments. Some patients do not show any response (primary non-response), and others show initial response but loss of response over time despite increased doses and/or more frequent administration of the drug (secondary loss of response). The absence of a therapeutic response can be related to the targeting of an inflammatory pathway, which is not the principal actor for the disease in an individual patient but is also often related to suboptimal dosing or unwanted immunogenicity of the therapeutic antibodies. The latter results in the formation of anti-drug antibodies (ADAs), which can lead to lower serum drug concentrations by neutralising the drug and/or by increasing its clearance. Importantly, subtherapeutic serum drug levels might also be caused by individual differences in drug bioavailability and pharmacokinetics.**[1]**

In the early years of antibody therapies, because of the lack of therapeutic alternatives, strategies to deal with primary non-response and secondary loss of response needed to be developed. Along with the expanding therapeutic armamentarium was a large potential for improved patient care. However, this might also open the door for “trial-and-error-medicine” with the risk of suboptimal care for a higher price, currently € 10,000 to € 20,000/year per patient. Indeed, clinical decision-making is nowadays often based on clinical symptoms alone, so when patients lose response, clinicians intensify treatment with the existing therapeutic antibody, and if no improvement occurs, treatment is empirically switched to another therapeutic antibody with the same (within-class) or a different (out-of-class) mechanism of action. More recently, (academic) clinicians have started to optimise treatment by adjusting the dose based on serum drug and ADA concentrations (i.e., therapeutic drug monitoring [TDM]) to reach the drug exposure associated with the highest possible response rate. Such a testing-based strategy has multiple advantages over the empiric approach because it allows for targeted dose adjustment in patients with low serum drug concentrations due to non-immunogenic pharmacokinetic mechanisms. **[2]** On one hand, it avoids dose escalation in patients who are unlikely to show response due to immunogenicity or mechanistic override, and on the other, some patients achieve remission while being overexposed to the drug, which increases the risk of side effects. Although many clinicians empirically use dose tapering, which may lead to a loss of response and flares in some cases. Therefore, TDM can also be used to taper the administered dose in patients with drug concentrations above the therapeutic window and in those in prolonged and sustained remission.

In addition to data on exposure–response relationships and therapeutic windows for several therapeutic antibodies, only a few prospective studies have analysed the incremental cost-effectiveness ratio of individual (TDM-based) dose adjustments as compared with usual care. The few studies available essentially based on modelling or retrospective studies showed a significant cost per quality-adjusted life year (QALY) gain. Comparative prospective cost-effectiveness studies are still lacking. Most of the studies published so far

support the interest of TDM in case of loss of response (reactive TDM).**[3]** Proactive TDM resulted in conflicting results in terms of clinical outcomes, **[4]** but may help tapering the dose while maintaining the response in patients with low disease activity, thus resulting in reduced cost.**[5]** Although several studies showed (indirect) evidence in favour of TDM-guided clinical decision-making, utilisation of TDM is complex, and dose optimisation is not intuitive. Therefore, individualised dose optimisation would benefit from the availability of supportive software, to make TDM cost-effective.

1.1.2 DESCRIPTION OF THE CHALLENGE (MAIN AIM)

Chronic inflammatory diseases (e.g., rheumatoid arthritis, Crohn's disease and psoriasis) have an overall prevalence of 5% to 7% in Western society, affecting both sexes, from children to older people. These diseases typically have an onset early in life, and with no cure available, patients require life-long treatment, which necessitates safe, tolerable and effective drugs. Treatment of these diseases has been revolutionised with the introduction of therapeutic antibodies. Unfortunately, a considerable proportion of patients do not show response to treatment or they lose response over time, which leads to overall poor drug persistence. In addition, not all patients achieve complete remission, mainly because of suboptimal dosing and immunogenicity that causes the development of ADAs, particularly anti-TNF antibodies. Furthermore, therapeutic antibodies exhibit considerable interpatient variability in pharmacokinetics, thus leading to a variability in clinical response.**[1]** Moreover, treatment with therapeutic antibodies is expensive and results in significant personal, societal and healthcare costs, even though biosimilars have reduced the cost by 20% to 34%.**[6]**

To overcome these problems, researchers and clinicians are focusing on several topics to improve patient care in treatment with therapeutic antibodies. First, stratification of patients before treatment ("which therapeutic antibody to use in a given patient") is becoming more important because some patients do not show response to certain therapeutic antibodies. However, until now, no such stratification signature has been identified, and more research is urgently needed. In contrast, some patients received supra-optimal doses, thus leading to over-exposure with poor outcomes (primary non-responders) in some cases, whereas some other patients achieve a remission state while being unnecessarily overexposed. TDM, "the use of drug concentrations to optimize the dose for an individual patient", is a clinical decision-making tool based on blood/serum drug and ADA concentrations that aims to improve treatment efficacy by providing individual guidance for more accurate use and dosing of therapeutic antibodies ("the right dose for the right patient").**[7]**

However, in Europe, expertise on optimising treatment with therapeutic antibodies for patients with chronic inflammatory diseases is highly fragmented and largely limited to a few pioneering academic hospitals and research centres. Transferring knowledge and techniques to other centres is challenging, because of the need for in-house expertise to efficiently interpret and translate TDM data for the benefit of the patient. Furthermore, each hospital/research centre uses its own TDM methodologies, protocols and assays, and this lack of standardisation in methods leads to a significant duplication of efforts and difficulties in comparing results across centres and hinders the setting up of multicentre clinical trials. Despite efforts to gather clinicians and pharmacometricians, TDM of therapeutic antibodies initiatives remains too isolated. Therefore, the main aim of this ENOTTA Action is to eliminate the barriers and raise awareness of the implementation of individualised (TDM-guided) dose optimisation of therapeutic antibodies for chronic inflammatory diseases in daily clinical practice, throughout Europe. This aim will be achieved by creating an interdisciplinary, pan-European network to coordinate, streamline, and set targets and guidance for future translational research in this area. The network will encompass all aspects of the challenge, gathering medical doctors, basic researchers, biologists, computer scientists, pharmacometricians, patients, small and medium entreprises (SME)s and health authorities.

In addition, such a network is essential in the context of the COVID-19 pandemic because patients with autoimmune diseases may lose contact with their physicians and may be at risk of severe drug-related complications, thus increasing the cost to society. ENOTTA will anticipate the scenarios that may affect, in any way, the use of therapeutic antibodies by securing continuous and effective TDM.

1.2 PROGRESS BEYOND THE STATE-OF-THE-ART

1.2.1 APPROACH TO THE CHALLENGE AND PROGRESS BEYOND THE STATE-OF-THE-ART

The objective of therapeutic antibodies is to control the inflammation, whatever the site (e.g., joints, skin or gastrointestinal tract), in the long term. However, therapeutic antibodies generate considerable costs in many European countries. For instance, in France, the amount allocated by health insurance was € 1.5 billion for all three main prescribing specialities (rheumatology, gastroenterology, dermatology). The annual expenditure for

rheumatoid arthritis patients is estimated to be three times higher than for patients who do not receive such treatment. Therefore, tools to predict and optimise the response before and at the start of treatment (patient stratification) will become more important to improve patient access to the best treatment and to reduce healthcare expenditures, which is especially important in the current situation of growing constraints on healthcare budgets worldwide.

Therapeutic antibodies belong to end-point treatments because they were developed to inhibit downstream effectors, such as TNF. In the last decade, a few centres across Europe and beyond have developed the concept of TDM in the setting of inflammatory disease with therapeutic antibodies. For this reason, the Action will focus on inflammatory diseases as a whole, breaking the fences between medical disciples by combining the "cytokine-based disease approach" with the traditional tissue-based disease paradigm.**[8]** Therefore, disease mechanisms will be assessed at the individual level to anticipate the treatment effect. Given the large accumulation of evidence in some diseases, the Action will focus, at least in the beginning, on Crohn's disease, rheumatoid arthritis and psoriasis, including the paediatric population, before extending to other conditions. Because the body of evidence for TNF inhibitors is large, the network will focus on full-length monoclonal antibodies (infliximab, adalimumab, golimumab), the fusion protein etanercept and the pegylated Fab certolizumab pegol.

Treatment optimisation by adjusting the dose of the therapeutic antibody, based on serum drug and ADA concentrations, to reach a drug exposure associated with the highest possible response rate, has multiple advantages over treatment adjustment based on clinical outcomes alone.**[2]** On one hand, TDM allows for targeted dose adjustment in patients with low serum drug concentrations due to non-immunogenic mechanisms, and on the other, it avoids dose escalation in patients who are unlikely to show response due to immunogenicity or mechanistic override. Furthermore, TDM can also be used to taper the administered dose in patients with drug concentrations above the therapeutic window in prolonged and sustained remission. Several studies have been performed, and in some countries, consensus papers and guidelines have been published.**[9]** These efforts are still scattered, and the intent of the Action is to address the efforts systematically. Innovation will be fostered by the development of increased access of researchers and clinicians to evidence-based guidelines and algorithms for individualised dose optimisation of therapeutic antibodies used in chronic inflammatory diseases.

Prospective randomised multicentre trials are needed to assess cost-effectiveness results of individual dose optimisation compared to standard care, to convince health authorities to allow flexible dosing, which is currently not permitted in most drug labels. Furthermore, to efficiently implement this evidence-based individualised dose optimisation, both clinicians and patients need to be educated and informed on the possibilities and benefits of this methodology. So far, few consensus guidelines have been published, essentially outside the EU in the field of inflammatory bowel disease.**[9]** The network will take advantage of these initiatives to harmonize the individualized intervention in dosing schedules in Europe.

In conclusion, a substantial improvement in patient care will be realised by implementing individualised TDM-guided dosing schemes for therapeutic antibodies in chronic inflammatory diseases. This move will ultimately result in a cost-effective and sustainable use of these expensive drugs. The Action will bring together researchers, clinicians, pharmacists, patients and other stakeholders to create an interdisciplinary, pan-European network to defragment the scientific research in this field and to coordinate, guide and set targets for future translational research. Such a networking structure will also facilitate the sharing of knowledge and promote the dissemination of knowledge throughout Europe.

The network will proceed beyond the state-of-the-art with the following:

1) A first focus of this Action will be patient stratification before and at the start of treatment to allocate the right drug to the right patient. The specificity of ENOTTA is to bring together specialists in predictive markers to tackle the molecular and pharmacological basis of individual variation in response to TNF inhibitors. A systems medicine approach will provide clinicians with objective indicators to which they can adapt treatment choices. This approach could be facilitated by meta-analysis of randomised controlled trials to identify patient characteristics such as demographics (age, sex, weight), molecular (-omics) and cellular profiles that are associated with response or non-response to a given therapeutic antibody. To achieve this goal, the consortium will examine the potential interest of implementing these covariables in the treatment choice.

2) Because each hospital/research centre uses its own TDM methodologies, protocols and assays, there is a strong need for an effective approach for harmonisation and standardisation of TDM assays. By introducing universal standards of the different assays, the quality and reproducibility of prospective multicentre clinical studies will improve significantly. The Action will also consider the relevance of point-of-care testing to

increase the acceptability and accessibility to TDM, particularly in the paediatric population. Almost all participants of the ENOTTA consortium have been committed to TDM in their hospital practice, at the bench or bedside.

3) Significant innovation is expected from computational population pharmacokinetic-pharmacodynamic models predicting treatment response and enabling individualised dose optimisation. The target concentration intervention (TCI) approach was introduced in 1999 and has gained recent interest in the scientific community.**[10]** It has been implemented in the field of small-molecule drugs, and some researchers consider TCI as the future way to optimise dosing regimens. The Action will examine the potential benefit and feasibility of the TCI principle applied to biopharmaceuticals. Therefore, experts in pharmacometrics are taking part in ENOTTA to provide a comprehensive analysis of the exposure–response relation.

4) The Action will assess TDM with a multidimensional–health technology assessment–approach. There is a dearth of data on cost-effectiveness and acceptability of TDM of biopharmaceuticals in chronic inflammatory diseases. The Action will investigate how TDM can make the cost of therapeutic antibodies per QALY remain lower than the willingness to pay. Regarding the acceptability of TDM of biopharmaceuticals, the data are almost absent. The shared decision between the physician and patient is considered essential by European societies but is still poorly studied. Its benefits in terms of observance and patient satisfaction has been suggested by several authors. ENOTTA will examine patients‘ perspectives in this respect. The access to digitalised results is an important aspect for both patients and physicians. This access must be secured and sped up with the help of advanced e-Health technologies. Experts in cost-effectiveness, specialists in data management, and SMEs in e-technologies are involved in the ENOTTA consortium for achieving this challenge.

5) The Action will consider the dissemination and sustainability of TDM by providing access to TDM platforms with all facilities throughout Europe, not just a few tertiary centres. This aspect will be developed in collaboration with epidemiologists, computer scientists and health authorities to bring TDM for use of the entire European community.

Taken together, the innovative nature of this Action will come from the ability of the whole group to create tools for patient stratification, assay harmonisation, universal standards and the availability of guidelines and treatment algorithms that are accepted by healthcare insurances, clinicians and patients. These developments will be crucial for implementing individualised (TDM-based) dose optimisation of therapeutic antibodies in daily clinical practice. Ultimately, the optimal use of therapeutic antibodies using TDM will alleviate the burden on the healthcare system. Furthermore, the insights obtained by this Action might also guide future research in other disciplines such as oncology that use therapeutic antibodies.

1.2.2 OBJECTIVES

1.2.2.1 Research Coordination Objectives

The main aim of this COST Action is to eliminate the barriers and raise awareness for implementation of individualised (TDM-guided) dose optimisation of therapeutic antibodies for chronic inflammatory diseases in daily clinical practice. To achieve this aim, the following Research Coordination Objectives will be pursued:

1) Create an interdisciplinary society of researchers, clinicians, experts and stakeholders in order to defragment the European research community working on dose optimisation of therapeutic antibodies.
2) Investigate and develop patient stratification tools to predict and optimise treatment with therapeutic antibodies, before and upon the start of treatment, with the contribution of predictive analytic companies or academic groups .
3) Develop guidelines for clinical management and best practices for individualised (TDM-guided) dose optimisation.
4) Improve the reproducibility, standardisation and harmonisation of TDM assays and protocols.
5) Set up a comprehensive and structured overview on the availability of patient data/samples (e.g., the number of patients receiving treatment, how many patients receive a certain therapeutic antibody, the number and quantity of well-documented (serum) samples), and the availability of TDM assays across all participating hospital/research centres.
6) Evaluate the cost-effectiveness of individualised (TDM-guided) dose optimisation of therapeutic antibodies as an instrument to reduce healthcare expenditures, thus ensuring access and affordability.
7) Investigate how TDM may be implemented and secured in the community with the support of e-Health SMEs.

8) Disseminate knowledge and findings within the scientific and clinical community and to policymakers .

1.2.2.2 Capacity-building Objectives

The main capacity-building goals of this Action are to develop the critical mass of researchers working on the topic by leveraging and embedding scientific excellence across the European TDM research community and by steering the future research agenda (**Table 1**). To achieve these goals, the Action will pursue the following the capacity-building objectives:

1) Facilitate scientific collaboration and knowledge exchange by organising and coordinating an open, sustainable, and multidisciplinary network using an electronic platform.
2) Stimulate the development of a joint research agenda to facilitate the development of new research projects, post-marketing studies and prospective multicentre clinical trials.
3) Offer a balanced vision and expertise to European and national decision-makers by their participation in the network as external advisors and by targeted communication measures.
4) Identify and interact with stakeholders. Stakeholders will be actively identified among Action members and their networks but also beyond.
5) Form an educational programme by organising training schools, workshops, and short-term scientific missions (STSMs) to offer training in different multidisciplinary areas embedded in this Action, allow for dissemination of knowledge and research outputs, and open opportunities to interact with and learn from more experienced research groups.
6) Help Young Researchers and Innovators (YRIs) and researchers from inclusiveness target countries (ITCs) develop and expand their professional networks, meet experts and stakeholders, and create opportunities for collaborations.
7) Support researcher mobility by encouraging YRIs and ITC researchers to participate in training schools and STSMs. The Action will strive for a fair and diverse membership and will promote gender equality.
8) Give the opportunity to SMEs and pharmaceutical companies to join the Action (pharmacometricians, biostatisticians, assay developers, software producers, data managers and clinical trial designers).

Table 1: Objectives of the ENOTTA Action

	Research Coordination	Capacity-building
Objectives:	Eliminate barriers and increase awareness for implementing individualised (TDM-guided) dose optimisation of therapeutic antibodies for chronic inflammatory diseases	Develop the critical mass of researchers working on the topic by leveraging and embedding scientific excellence across the European TDM research community and by steering the future research agenda
Specific (what are the precise methods and expertise)	Brain storming within multidisciplinary WG to avoid specialist self-enclosure. The network gathers keys specialists in particular clinical sciences, pharmacometrics and biology. Educational programs for healthcare providers and patients will be delivered.	Number of cooperations between academics from different fields and between academic and non-academic members (European patient associations, healthcare providers, SMEs, companies, governments)
Measurable (how to monitor the work in progress)	European guidelines will emerge from the network. The number of TDM platforms across Europe will account for the spread of the Action.	Research programs will be developed within ENOTTA. Involvement of non-academic entities for research and teaching purposes.
Achievable (how confident we are to attain our objective)	Ability of each WG member to cross-talk with other field counterparts. WG leader ability to cover all the multi-disciplinary aspects of the WG.	Network within countries between researchers and stakeholders

Relevant (what will be the impact of the objective once attained)	Position papers and guidelines throughout Europe will foster the dissemination of TDM of therapeutic antibodies. This will facilitate further trans-European collaborations in this field.	SMEs and biotech involved in collaborative projects along with academics.
Timely (how sure we are to reach the objective during the time frame)	Remote meeting every month as well as face-to-face sessions during general assemblies	Remote meeting every month as well as face-to-face sessions during general assemblies.

2 NETWORKING EXCELLENCE

2.1 ADDED VALUE OF NETWORKING IN S&T EXCELLENCE

2.1.1 ADDED VALUE IN RELATION TO EXISTING EFFORTS AT EUROPEAN AND/OR INTERNATIONAL LEVEL

This Action does not replicate any existing effort, and it is therefore unique in its breadth and depth. Indeed, to the best of our knowledge, there are no similar ongoing or past European projects/scientific networks that have been dealing with individualised (TDM-guided) treatment optimisation of therapeutic antibodies for chronic inflammatory diseases. In the past, the EU has also supported several research projects on therapeutic antibodies, including projects focusing on drug immunogenicity (Innovative Medicines Initiative [IMI] ABIRISK, and profiling of [non]-response to therapeutic antibodies [FP7 PRIAT]). Also, other initiatives such as the European Working Group on Immune Mediated Inflammatory Diseases (ewIMID) and the European Immunogenicity Platform (EIP) focusses on targeted therapies in chronic inflammatory diseases and immunogenicity of therapeutic antibodies. Importantly, most of the aforementioned projects are no longer active and have not focused on TDM as such. Also, despite some initiatives to create specific study groups, no initiative/project has gathered a critical, pluri-disciplinary mass of researchers and knowledge to become a globally leading contributor to the scientific field. Therefore this COST Action is ideally placed to fulfill this need.

2.2 ADDED VALUE OF NETWORKING IN IMPACT

2.2.1 SECURING THE CRITICAL MASS AND EXPERTISE

One of the main facts responsible for the slow development of individualised (TDM-guided) treatment algorithms for therapeutic antibodies in chronic inflammatory diseases, despite their wide use, is that the current research groups currently involved in this domain are highly scattered throughout Europe and these research groups are of limited size. Furthermore, several projects on this topic are nationally funded, but none will bring together the required expertise into one single critical mass of knowledge and people. The stakeholders involved in ENOTTA are academic institutions, hospitals, scientific European societies, patient organisations and health ministries). For these reasons, reaching the main aim of this Action depends on the creation of a European multidisciplinary network, bringing together experts from different fields, such as clinicians specialised in different chronic diseases, translational researchers and assay developers, pharmacometricians and pharmaco-economists. The Action will provide a framework to network, maintain and expand a collaboration of its participants within Europe. Such a structure will facilitate sharing of know how and promote the dissemination of knowledge and therefore act as a catalyst in this research area by fostering scientific collaboration between key players in the European research area and by establishing links with leading experts worldwide.

2.2.2 INVOLVEMENT OF STAKEHOLDERS

The Action aims to set up a pan-European network of scientists focusing on evidence-based optimisation of therapeutic antibody treatment for chronic inflammatory diseases by patient stratification and standardisation and clinical implementation of TDM. As a consequence, many stakeholders are connected to this Action:

1) Biopharmaceutical/biomedical researchers/assay developers and clinicians from different fields; in particular in the field of rheumatic diseases, inflammatory bowel diseases, psoriasis and paediatrics counterparts constitute the majority of the network. Their main interest is to optimise the treatment of patients with chronic inflammatory diseases that are treated with therapeutic antibodies, using the above-mentioned tools. They will contribute to and benefit from knowledge defragmentation, obtained insights and

scientific discussions. International key societies, such as the International Association of Therapeutic Drug Monitoring and Clinical Toxicology (IATDMCT) or European Association for Clinical Pharmacology and Therapeutics (EACPT), will be included in scientific discussions for the implementation of TDM. Pharmacometricians will use this knowledge as input for the development of computational predictive models and simulation software that enables individualised dosing (dose optimisation). Pharmaco-economists involved in ENOTTA will assess the efficiency of TDM compared to usual care.

2) Pharmaceutical and diagnostic companies interested in the development of new assays guiding patient stratification and/or treatment optimisation and in companion diagnostic tests will be contacted to attend the kick-off meeting.

3) The (long-term) end-users benefitting from the network are clinicians and patients (represented by patient organisations), who will benefit from guidelines, patient stratification tools, standardised TDM assays and simulation software that can guide dose optimisation and improve treatment outcomes. Furthermore, patient organisations will be important in giving patients access to information about their treatments. Therefore, major European and International patient clinician/patient societies and national clinician/patient organisations will be involved in the Action. Examples are national organisations of people with arthritis/rheumatism (PARE) and the European Federation of Crohn's and ulcerative Colitis Associations (EFCCA). The interaction with these organisations is crucial to disseminate the findings of the COST Action and influence guidelines and recommendations through Position Papers.

4) Finally, also national and international policymakers, healthcare and research funders will be involved because they are essential in setting policy to implement the evidence-based cost-effective optimisation of treatment with therapeutic antibodies, and they are responsible for providing optimal access to these drugs for their inhabitants.

The Action's stakeholders will be involved via active participation in the Action and targeted communication measures. The plan to attract and inform scientific and industrial stakeholders will be complemented by making contacts with European, international and national clinical and patient societies and to disseminate the results within these societies. Finally, during the course of this Action, national and international policymakers, healthcare and research funders will be involved gradually in the discussions fostered by this Action, to inform the participating researchers and to be informed by the developed ideas from the Action's activities. From the start of the Action, contacts will be established by each of the scientific partners in the Action with key policymakers in their own country, the EU and international agencies.

3 IMPACT

3.1 IMPACT ON SCIENCE, SOCIETY AND COMPETITIVENESS, AND POTENTIAL FOR INNOVATION/BREAK-THROUGHS

3.1.1 SCIENTIFIC, TECHNOLOGICAL, AND/OR SOCIOECONOMIC IMPACTS (INCLUDING POTENTIAL INNOVATIONS AND/OR BREAKTHROUGHS)

Scientific impact and potential innovation
This COST Action will enable the creation of a scientific community for optimisation of treatment with therapeutic antibodies for chronic inflammatory diseases. For the researchers and clinicians involved in the network, this Action presents an opportunity to expand their professional networks and to establish new collaborations and initiate new research projects. Also, it will enable YRIs and researchers from less research-intensive countries to interact with and share knowledge and skills with established researchers in the field. Concerted research activities enabled by this Action will increase knowledge on optimal patient stratification, (TDM-guided) dose optimisation, and standardisation of TDM assays. This creation of new knowledge and development of guidelines will enable researchers, clinicians and health authorities to make evidence-based decisions on the use and optimisation of treatment with therapeutic antibodies. In the long-term, a more thorough understanding of the mechanism of action of therapeutic antibodies will provide more knowledge in the pathophysiology of chronic inflammatory diseases. Furthermore, results obtained by the research activities embedded in this Action can at a later phase be used as a basis to extend treatment optimisation of therapeutic antibodies for other diseases, such as cancer, metabolic or infectious diseases.

A potential risk associated with these new treatment algorithms/individualised dose optimisation strategies is that these will possibly not be accepted to the desired degree by clinicians. This risk will be mitigated by *in silico* simulation approaches to facilitate the setting-up of Europenan prospective randomised multicentre clinical trials to investigate whether patient stratification and (TDM-guided) individual dose optimisation are

clinically and/or cost-effectively superior to usual care. Results of these trials will be used to convince health authorities to allow flexible dosing of therapeutic antibodies in clinical pratice. To efficiently implement individualised dose optimisation, clinicians and patients will be educated and informed of the possibilities and benefits of this methodology.

Technological impact and potential innovation
This Action will improve the comparability and reproducibility of TDM assays and results across different hospitals/research centres. This standardisation will benefit clinicians and researchers who generate and work with the data. Also, pharmaceutical and diagnostic companies will develop new assays and companion diagnostic tests (for patient stratification and treatment optimisation). In the long-term, population pharmacokinetic-pharmacodynamic models and simulations will be the basis for the development of tools to facilitate individualised treatment/dose optimisation of therapeutic antibodies. The development of these tools will be an important step for wide implementation of individualised (TDM-guided) treatment optimisation in daily clinical practice. The implementation of TDM will be at the agenda of the Action, once sufficient evidence has been gathered. This step will require the support of computer scientists/companies with expertise in information and communications technology by creating an electronic platform for exchange of knowledge on TDM. The Action will enable the mutual use of the developed tools by clinicians and researchers.

One risk associated with this potential breakthrough is that not all research centres in the Action will cooperate in this standardisation effort. However, this risk is very low in that most assay providers are interested because this effort will facilitate interpretation of results. Another risk is the possibility that population pharmacokinetic-pharmacodynamic models cannot be developed or at least not within the Action's timeframe. However, this risk is also limited because the development of such computational models is realistic given the experienced pharmacometricians involved in the Action, and some models have already been published in the last couple of years. The risk of not obtaining enough data for development of these models is mitigated by collaborations between the members of the network. A last associated risk is a possible regulatory and/or legal reluctance to use and implement the developed models/tools for individualised dose optimisation. This risk will be mitigated by involving regulatory and legal authorities early during the Action.

Socioeconomic impact and potential innovation:
This Action will establish a European community of experts working on individualised (TDM-guided) treatment/dose optimisation of therapeutic antibodies for chronic inflammatory diseases. This community of experts will support researchers, clinicians and patient organisations by giving information, developing guidelines and best practices and training about treatment optimisation of therapeutic antibodies, for example on how to best perform patient stratification and how to optimise the dose for an individual patient but also how to interpret serum drug or ADA concentrations. The Action will also have an impact on all patients with chronic inflammatory diseases because individualised treatment optimisation will have a significant effect on their disease activity and thus also their quality of life and work/school productivity. Furthermore, treatment optimisation will reduce hospitalisations and treatment expenses as well as drug persistance.

If accepted and fully adopted, the results of this Action will enable a better access and optimized use of therapeutic antibodies for all European patients with chronic inflammatory diseases. The risk level is considered low because policymakers and healthcare providers will be involved early during the course of the Action and will be informed and updated on all Action results and achievements.

3.2 MEASURES TO MAXIMISE IMPACT

3.2.1 KNOWLEDGE CREATION, TRANSFER OF KNOWLEDGE AND CAREER DEVELOPMENT

This network represents a diverse group within the fields of TDM and assay development, molecular and translational researchers, pharmacometricians, pharmaco-economists, health economists, computer scientists, information and communications technology experts and clinicians in gastroenterology and rheumatology. Because this Action focuses on all chronic inflammatory diseases for which therapeutic antibodies are being used, collaborations will also be sought with dermatologists and paediatricians. Furthermore, data managers need to be included in the Action. During the planning of the Action, the Network of Proposers included members with proven and successful track records in basic, translational and clinical research, development and innovation but also a high number of early- to mid-career researchers who will be encouraged to take a leading role in the Action. YRIs, researchers and teachers will set up in their institutions specific workshops and courses on TDM of biopharmaceuticals in the field of inflammatory diseases and beyond. Also, YRIs will receive important knowledge and establish potentially long-lasting contacts for future collaborations by participating in meetings, workshops, training schools and STSMs. This network will be able to provide expertise and resources required to achieve the objectives of the Action because they have access

to outstanding research facilities and diverse patient groups and extensive experience in conducting research projects and clinical studies. This will allow for applying the Action's conceptual, harmonisation and strategic work directly to empirical studies and feed their findings back into the Action. Another important aspect of the network is the promotion of collaboration with industrial partners (assay developers, pharmacometricians, software producers, data managers, clinical trial designers), which will improve the commercial application and exploitation of technologies in this Action. The Action will embrace stakeholders such as European patient associations and scientific/clinical societies, at national and European levels. Taken together, this Action ensures the development of the critical mass of researchers and stakeholders, with experts from different research domains that guarantee the transmission of knowledge and therefore the achievement of the objectives of this Action. As the Action progresses, the Network will be expanded by actively recruiting new members, next to the self-application of interested individuals. The exploitable results of the Action will consist of knowledge in various domains. This will include the identification of predictive models for clinical guidance ("the right drug for the right patient") and for dosing ("the right dose for the right patient"). Given the number of patients with inflammatory chronic diseases, this knowledge could be transferred to SMEs for biological or data analyses to produce predictive tools for patient stratification and TDM purposes. Thus, the Action will foster interactions between academic and non-academic sectors.

3.2.2 PLAN FOR DISSEMINATION AND/OR EXPLOITATION AND DIALOGUE WITH THE GENERAL PUBLIC OR POLICYMAKERS

To maximise the impact of the Action, a specific Working Group (WG5) will be dedicated to disseminating and the sustainability of the results of the Action. To this end, the leaders of this WG will closely interact with the Action Management Committee (MC) and the leaders of WGs 1-4.

Dissemination

- Electronic communication:
  - A designated website will be set up for spreading the objectives of the Action. Furthermore, the website will contain all the Action outputs (links to open access scientific papers, guidelines for clinical management, best practices, presentations, etc.) and activities (meetings, training schools, workshops, STSMs, etc.). The website will have an open and closed part for external (i.e., for all stakeholders and interested parties) and internal (i.e., for network, management committee (MC)) communication, respectively. An inventory of all TDM platforms available throughout Europe will be updated on a regular basis. Hence, a pan-European heath technology assessment on TDM will be facilitated.
  - A newsletter highlighting network activities and findings will be published twice a year on the website. This newsletter will also be sent to a mailing list containing all MC participants and other interested individuals (with an option to subscribe to the mailing list on the Action website). To create a multiplier effect, all MC participants will be asked to commit to forwarding the newsletter to their personal network.
  - An Action flyer, containing information on the objectives of the Action, will be used to actively reach out to European, international and national patient societies.
  - The network will also be active on social media and professional networks, to reach out to YRIs, patients, etc.
- Publications:
  - Publications in peer-reviewed scientific journals, which will be adopted as state-of-the-art by international researchers/clinicians and researchers/clinicians not (yet) involved in the Action. To widen exposure, the Action will adopt the Horizon 2020 open access policy.
  - Publication of research and clinical guidelines on TDM, which will be adopted by clinicians in randomised controlled trials but also in daily clinical practice.
  - Publication of white papers to reach out to policymakers.
  - Targeting of mainstream media via institutional press and media services.
- Face-to-face dissemination
  - MC and WG meetings facilitate communication among Action participants.
  - Organisation of workshops and training schools in which participants will be able to gain and exchange expertise. Workshops and training schools are open to YRIIs, ITC researchers/clinicians and more established researchers who will benefit from the training and bring knowledge back to their institution. The topics will be diverse in order to encompass all the aspects of the Action, from therapeutic antibodies production, pharmacometrics, clinical structures of tertiary care centres, assay development, etc. Pharmaceutical companies will be invited during a dedicated workshop.
  - STSMs organised by the Action will facilitate the movement of YRIs and ITC researchers/clinicians in order to increase the exchange of expertise and knowledge.
  - Regular seminars and webinars and at least one massive open online course (MOOC) will be organised. These events will be promoted to all stakeholders, international experts, relevant healthcare authorities and policymakers to facilitate communication between the involved parties.

- The Action will organise a final conference to highlight and disseminate the results of the Action. This conference will focus on results obtained by the Action, and participation of all stakeholders will be encouraged in the newsletter and website, by personal invitation, etc.
- Action results will be presented (posters and presentations) at international scientific conferences organized by international consortia such as European Crohn and Colitis (ECCO), European Alliance of Associations for Rheumatology (EULAR) and European Academy of Dermatology and Venereology (EADV), etc., aiming to provide a direct interaction with other members of the scientific community and pharmaceutical/diagnostic companies, to raise awareness of the Action in different target groups and attracting additional stakeholders to participate in the Action.
- In addition, the Action will participate in symposia organized by non-academic partners to foster collaboration between the academics and SMEs or pharmaceutical companies.

Exploitation
This Action does not focus on the development of a specific product, but rather on networking and the establishment of new connections and collaborations. The main exploitable results from the Action are new insights obtained from discussions, knowledge defragmentation and new collaborations between network members. Expert advice on the protection of intellectual property (IP) will be available within the network. In any case, the Action will strive to exploit and disseminate the obtained results as widely and efficiently as possible. Indirectly, the Action will also contribute to advances that may lead to exploitable results in specific research projects funded through other sources. In that case, protection of IP for a given project will be in accordance with the specific member institutions or project funding agencies' rules and guidelines. Non-disclosure agreements will be used in case-sensitive material with respect to IP rights or confidentiality presented during meetings. All stakeholders in the Action will align with the Responsible Research and Innovation *(*RRI) principles. The ENOTTA Action will try to promote institutional changes in monitoring patients receiving therapeutic antibodies.

4 IMPLEMENTATION

4.1 COHERENCE AND EFFECTIVENESS OF THE WORK PLAN

4.1.1 DESCRIPTION OF WORKING GROUPS, TASKS AND ACTIVITIES

Five WGs have been identified. Each WG is involved in the analysis and development of specific topics. Strong collaborations between the WGs will be encouraged to achieve the Action's objectives. Furthermore, if specific expertise and/or expansion of the WG is needed, collaborations within and outside the Action will be actively sought.

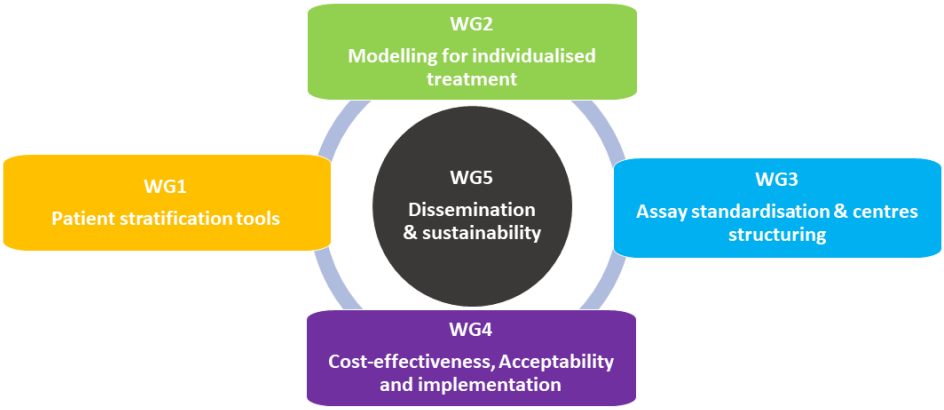

Figure 1: Working groups of ENOTTA Action

WG1 – Patient stratification tools for optimal treatment with therapeutic antibodies
Objectives: This WG will investigate how to optimally stratify patients before treatment ("which therapeutic antibody to use for a particular patient") and at start of treatment ("which therapeutic antibody dose to use for a particular patient").
Tasks and activities:
- T1: Initiate collaborations (with help of structured overview of participating hospitals/research centres from WG3) for (retrospective) data analysis.

- T2: Investigate and identify molecular and/or cellular profiles to predict response to therapy with a certain therapeutic antibody before the start of treatment.
- T3: Investigate and identify patient characteristics/covariates that predict the best starting dose of treatment with a certain therapeutic antibody in a certain patient for maximal treatment response.
- T4: Develop guidelines on how to optimally stratify patients before and at the start of treatment with therapeutic antibodies to allocate the right drug at the right dose to the right patient.

WG2 – Individualised (TDM-guided) treatment optimisation of therapeutic antibodies
Objectives:
This WG will investigate the individualised treatment optimisation of therapeutic antibodies in chronic inflammatory diseases. More specifically, this WG will focus on deriving therapeutic windows for different therapeutic antibodies in different diseases from large patient cohorts, developing population pharmacokinetic-pharmacodynamic models and simulations, and deducing guidelines/algorithms for TDM-guided dose optimisation. This will require the selection of the most relevant data, such as patient/disease characteristics, clinical outcomes, surrogate markers of disease activity, time point for blood sampling etc., that will be useful for pharmacokinetic-pharmacodynamic analyses.

Tasks and activities:
- T1: Collect information from previously performed studies on therapeutic windows of different therapeutic antibodies in chronic inflammatory diseases, review the state-of-the-art and identify remaining knowledge gaps.
- T2: Initiate collaborations (with help of structured overview on participating hospitals/research centres from WG3) for (retrospective) data analysis.
- T3: Establish an optimal therapeutic window for the different therapeutic antibodies used in different chronic inflammatory diseases.
- T5: Develop population pharmacokinetic-pharmacodynamic models and simulations for the different therapeutic antibodies used in the different diseases.
- T7: Develop guidelines on dose optimisation of therapeutic antibodies to reach serum drug concentrations within the therapeutic window for an optimal response to treatment.

WG3 – Assay standardisation and structured overview on participating hospitals/research centres
Objectives:
This WG will be responsible for several overarching activities needed for an optimal functioning of WG1 and WG2. First, this WG will investigate and implement measures for the harmonisation and standardisation of TDM assays to be able to compare the results of different hospitals/research centres. Second, WG3 will be responsible for setting up a comprehensive overview of patient data/samples that could be used to facilitate multicentre clinical trials (e.g., the number of chronic inflammatory disease patients receiving treatment within each participating hospital/research centre, how many patients receive a certain therapeutic antibody, the number and quantity of well-documented (serum) samples available for retrospective analyses, the availability of TDM assays, etc.) but without sharing the patient data/samples themselves. This structured overview will be important to find partners for setting up large retrospective and prospective multicentre trials because it will provide detailed information on how many patients could be included from each hospital/research centre. The design of the clinical study is a huge effort that needs staff and the commitment of hospitals (clinicians, experts in modelling, pharmaco-economists, laboratories, etc.).

Tasks and activities:
- T1: Evaluate the differences between available TDM assays for measuring serum drug and ADA concentrations to harmonise procedures and propose universal standards.
- T2: Coordinate laboratory sample exchange programmes as external quality control.
- T3: Select the most relevant markers of disease activity and quality of life
- T4: Collect data from the participating hospitals/research centres on number of patients, number of well documented samples, availability of TDM assays, etc. by mailings and questionnaires.
- T5: Set up and regularly update an overview of the above-mentioned data on participating hospitals/research centres (number of patients, number of samples, availability of TDM assays, etc.) in a database format, to be made available to the network members on the Action website.
- T6: Explore the feasibility of e-Health in the perspective of setting up a European funded application (research agenda), with the support of the *Digital health data and services – the European health data space*.

WG4 – Cost-effectiveness assessment, acceptability and implementation
Objectives:
The ultimate goal of the WG4 is to increase the awareness of the importance of the cost-effectiveness of TDM of inflammatory diseases. In addition, the WG will encompass the acceptability and affordability aspect of TDM by both patients and caregivers. To this end, experts on cost-effectiveness will be at the front line to catalyse the Action toward this essential aspect of TDM of therapeutic antibodies. WG3 will select the relevant outcomes in terms of clinical efficacy and quality of life. This WG4 will be connected with WG2 to simulate cost-effectiveness by computing absolute costs and QALYs between individualised TDM dosing and the current practice. The WG4 will also be in charge of evaluating the acceptability of TDM by patients and physicians
The shared decision between the physician and patient could benefit from observance and the patient's satisfaction with TDM. Furthermore, patients' preferences and empowerment are recognised as an important aspect in treatment management. Thus, WG4 will set up a research agenda on TDM acceptability and affordability by gathering both patient and caregiver perspectives. This will anticipate the hurdles for further implementation of TDM, in connection with WG5.

Tasks and activities:
- T1: Exchange knowledge about the existing cost-effectiveness studies of TDM.
- T2: Create a framework and health economic model for the international evaluation of cost-effectiveness of TDM.
- T3: Educate health authorities, physicians, and patients about the importance of TDM and its cost-effectiveness evaluation.
- T4: Exchange knowledge about existing patients' preferences and empowerment studies in the context of chronic inflammatory diseases.
- T5: Perform quantitative and qualitative studies (i.e., revealed preference methods), with the support of European patient associations (clinicians, nurses, pharmacists) to tackle patients' expectations and preferences.
- T6: Create a round table on patients' preferences and empowerment of TDM, gathering patients and care providers (clinicians, nurses, pharmacists).
- T7: Inform health authorities, educate physicians and patients about the importance of patients' preferences and empowerment in the field of chronic inflammatory diseases.

WG5 – Dissemination, & sustainability
Objectives:
This WG focuses on coordinating all communication and dissemination activities of the Action via the website, social media, open access journals, etc. The Action's website and social media serve as the main communication channels between Action members and stakeholders. Furthermore, this WG will be responsible for training YRIs and organising educational activities within the Action.

Tasks and activities:
- T1: Set up and maintain a website as a dissemination and internal communication platform.
- T2: Create a professional social-media account (e.g., LinkedIn) to keep professional stakeholders updated about the Action.
- T3: Create and distribute newsletters, posters, factsheets and leaflets to present findings in a condensed format (appropriate and adjusted to each group of stakeholders).
- T4: Coordinate the publication of reviews, protocols, position papers, etc.
- T5: Provide patient testimonies and short educational videos on TDM, subtitled in multiple languages, with a specific attention given to children with inflammatory diseases.
- T6: Organise seminars, webinars, at least one MOOC and a conference on treatment optimisation of therapeutic antibodies (in close collaboration with WG1-4).
- T7: Coordinate the organisation of training schools (in close collaboration with WGs 1-4).
- T8: Coordinate the organisation of STSMs.

4.1.2 DESCRIPTION OF DELIVERABLES AND TIMEFRAME

WG1 – Patient stratification tools for optimal treatment with therapeutic antibodies
Deliverables:
- D1: Publication of scientific paper(s) on identified molecular and/or cellular profiles predicting treatment response.
- D2: Publication of scientific paper(s) on identified patient characteristics/covariates predicting the optimal starting dose of a certain therapeutic antibody in a certain patient.

- D3: Publication of guidelines on optimal patient stratification.
- D4: Publication of white paper on guidelines for patient stratification.
- D5: Submission of at least 1 new collaborative research project proposal.

WG2 – Individualised (TDM-guided) treatment optimisation of therapeutic antibodies
Deliverables:
- D1: Publication of review(s) on the state-of-the-art and remaining knowledge gaps on therapeutic windows of therapeutic antibodies in chronic inflammatory diseases.
- D2: Publications on therapeutic windows of therapeutic antibodies used in the different chronic inflammatory diseases.
- D4: Publications on the population pharmacokinetic-pharmacodynamic models and simulation for therapeutic antibodies in different diseases.
- D5: Publication of guidelines on individualised TDM-guided dose optimisation.
- D6: Submission of at least 1 new collaborative research project proposal.

WG3 – Assay standardisation and structured overview on participating hospitals/research centres
Deliverables:
- D1: Publication of scientific papers on the differences between the available TDM assays and how the results obtained by each TDM assay can be compared to the other available assays.
- D2: Proposal of universal standards for TDM assays of each therapeutic antibody.
- D3: Sending out a standard questionnaire (PRO: patient reported outcomes) for collecting data on the available patients/samples and TDM assays to the participating hospitals/research centres.
- D4: Publication of a structured and regularly updated overview of hospitals/research centres interested to participate in multicentre studies on the Action website.

WG4 – Cost-effectiveness assessment, acceptability and implementation
Deliverables:
- D1: Publication of systematic literature review on cost-effectiveness of TDM of therapeutic antibodies in inflammatory diseases.
- D2: Identification of outcomes pertaining to cost-effectiveness, disease activity score, and quality of life that could be used for cost-effectiveness analyses.
- D3: Publication of guidelines on how to perform an effective cost-effectiveness study of TDM.
- D4: Publication of a perspective paper on acceptability and affordability of TDM of therapeutic antibodies in chronic inflammatory diseases.
- D5: Publication of patients' preferences and empowerment round table on TDM of therapeutic antibodies

WG5 – Dissemination and sustainability
Deliverables:.
- D1: Website fully functioning and online.
- D2: Social media profiles online.
- D3: Publication and mailing of six-monthly Action newsletter.
- D4: Report on STSM calls.
- D5: Report on the two training schools per year (starting from Year 2).
- D6: Report on the yearly workshop.
- D7: Report on the final Action conference.

The timeline for all the deliverables are not yet indicated but each WG will be responsible for drafting and implementing a work plan during their first WG meeting.

4.1.3 RISK ANALYSIS AND CONTINGENCY PLANS

Table 1: Contincency plan of the ENOTTA Action

Risk description	Contingency plan
Not reaching expected network participation	Ten proposers. Active recruitment with set target numbers for gender balance, YRI and geographical coverage. Contact with scientific societies of clinicians and basic scientists (rheumatology,

	gastroenterology, dermatology, immunology, pharmacology, computer sciences)
Cost or time overrun	Updating the Action plan with tougher planning.
Isolation of different disciplines in separate WGs	Organising joint WG meetings and inviting international experts who conduct interdisciplinary research.
Low interaction between participants (and between WGs)	WG leaders and Action MC will supervise quarterly the presence of an active and interdisciplinary participation within the WGs.
Incoherent WG work plan	Work plan adaptation by WG leaders and Action MC.
Delays in reaching deliverables	Discussion at MC meeting and/or intensive communication (tele/videoconference, email, etc.) and work follow-up by WG leaders and Action MC, allowing adjustment of effort to ensure deliverables are reached in a timely fashion.
Unsatisfactory scientific results	Work plan adaptation by WG Leaders and Action MC, search for alternative methods.
Exploitation and/or dissemination conflict	Thorough discussion of possible conflicts and recording in an agreement at the beginning of each project and during data collection. If necessary, mediation by an independent Action MC representative.
Low or insufficient impact of dissemination activities	Proactive interaction with stakeholders, coordinated by WG leaders, to maximise impact.

4.1.4 GANTT DIAGRAM

In this diagram, face-to-face meetings, if feasible, are indicated in green, and teleconferences are indicated in blue. WG tasks and deliverables are not indicated in this diagram because each WG will be responsible for drafting and implementing a work plan during the first WG meeting. As displayed in the WG scheme, inter-WG sessions will remain during each WG meeting, in particular, between WGs 1, 3 and 5 and between WGs 2 and 4.

	Year 1				Year 2				Year 3				Year 4			
Network activities	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4
Annual Network meeting																
Management Committee meeting																
Working Group meeting																
Dissemination and education																
Website online																
Newsletter																
Social media profiles online																
Organisation of STSMs																
Organisation of Training Schools																
Organisation of Workshops																
Organisation of Action Conference																

Figure 2: Gantt chart of the ENOTTA Action

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