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Deepak R. Jadon, Vinod Chandran, Alexis Ogdie, Stephen R. Pennington, Carmel Stober, Dafna D. Gladman, Maarten de Wit, Denis O'Sullivan, Philip Mease, April W. Armstrong, Kristina Callis Duffin, Conor Magee, Philip Helliwell, Christopher T. Ritchlin*, Oliver FitzGerald*

*Prof. FitzGerald and Prof. Ritchlin are joint senior authors.

ABSTRACT: The Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA)-Collaborative Research Network (CRN) intends to launch and secure funding for 3 pilot projects related to psoriatic disease, psoriatic arthritis (PsA), and cutaneous psoriasis (PsC). The first pilot project, a PsA Biomarkers for Joint Damage (BioDAM) pilot, will seek to determine the independent predictive ability of serum biomarkers for joint damage in PsA. The second pilot project will aim to identify predictors of the development of PsA among patients with PsC. The third pilot project will aim to identify biomarkers that predict treatment response in PsA and PsC. These pilot projects will prompt the development of clinical protocols to operate across participating centres, lead to the development of standard operating procedures for the collection and transport of biosamples across international borders, and begin to establish administrative and managerial structures for the CRN. The CRN hopes that the successful completion and research outputs of these 3 pilot projects will demonstrate the CRN's value to prospective collaborators and sponsors and thereby secure sustainable long-term funding.

Key Indexing Terms: Psoriatic Arthritis, Psoriasis, Biomarkers, Research, Imaging, Outcome Measures

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Author Information: DR Jadon, MBBCh, MRCP, PhD, Director of Rheumatology Research Unit, Cambridge University Hospitals NHS Foundation Trust, Cambridge, United Kingdom, dj351@medschl.cam.ac.uk; V Chandran, MBBS, MD, DM, PhD, Department of Medicine, Division of Rheumatology, University of Toronto, Toronto Western Hospital, Krembil Research Institute, Toronto, Ontario, Canada, Vinod.Chandran@uhnresearch.ca; A Ogdie, MD, Assistant Professor of Medicine and Epidemiology, Perelman School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania, USA, alexis.ogdie@uphs.upenn.edu; SR Pennington, Professor of Proteomics, PhD, Conway Institute for Biomolecular Research, University College Dublin, Dublin, Ireland, Stephen.Pennington@ucd.ie; C Stober, PhD, MBChB, MRCP, Consultant Rheumatologist, Cambridge University Hospitals NHS Foundation Trust, Cambridge, United Kingdom, carmel.stober@addenbrookes.nhs.uk; DD Gladman, MD, FRCPC, Professor of Medicine, University of Toronto, Senior Scientist, Krembil Research Institute, Toronto Western Hospital, Toronto, Ontario, Canada, dafna.gladman@utoronto.ca; M de Wit, PhD, Patient Research Partner, Department of Medical Humanities, Amsterdam University Medical Centre, Amsterdam, The Netherlands, martinusdewit@hotmail.com; D O'Sullivan, BE, Patient Research Partner, Our Lady's Hospice and Care Services, Dublin, Ireland, denis_osullivan@ymail.com; PJ Mease, MD, Rheumatology Research, Swedish Medical Center/Providence-St. Joseph Health, Seattle, Washington, USA, pmease@philipmease.com; AW Armstrong, MD, MPH, University of Southern California, Los Angeles, California, USA, aprilarmstrong@post.harvard.edu; K Callis Duffin, MD, University of Utah, Salt Lake City, Utah, USA, Kristina.callis@hsc.utah.edu; C Magee, MB, BAO, BCh, St. Vincent's University Hospital, Dublin, Ireland, conormagee@hotmail.com; PS Helliwell, DM, PhD, FRCP, University of Leeds, and Bradford Hospitals NHS Foundation Trust, P.Helliwell@leeds.ac.uk; CT Ritchlin, MD, MPH, Professor of Medicine, Division of Allergy, Immunology, and Rheumatology, University of Rochester Medical Center, Rochester, New York, USA, christopher_ritchlin@urmc.rochester.edu; O FitzGerald, MD, FRCPI, FRCP(UK), Newman Clinical Research Professor, Department of Rheumatology, St.

Vincent's University Hospital and Conway Institute for Biomolecular Research, University College Dublin, Dublin, Ireland, oliver.fitzgerald@ucd.ie

Corresponding Author: Deepak R Jadon, MBBCh, MRCP, PhD, Director of the Rheumatology Research Unit, Cambridge University Hospitals NHSFT, Addenbrooke's Hospital, Hills Road, Cambridge, CB2 0QQ, United Kingdom, phone +44 1223 217459; email dj351@medschl.cam.ac.uk

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Background

The Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA)-Collaborative Research Network (CRN) held its second meeting at the GRAPPA 2018 annual meeting in Toronto, Ontario, Canada. The CRN meeting was organized by a committee co-chaired by Professors Oliver FitzGerald and Christopher Ritchlin. The meeting was attended by 28 rheumatologists, 3 dermatologists, 6 patient research partners (PRP), 1 non-medical scientist, and 14 leads from the pharmaceutical industry.

The meeting's objectives were to discuss launching and securing funding for 3 pilot projects under the auspices of the GRAPPA-CRN. These pilots would: (1) prompt the development of clinical protocols to operate across participating centres; (2) lead to the development of standard operating procedures (SOP) for the collection, storage, and transport of biosamples; (3) begin to establish administrative and managerial structures for the CRN; and (4) ultimately demonstrate the CRN's value, which would encourage new centres to contribute and new sponsors to support the CRN. The long-term goal of securing more sustainable funding was also discussed and was inspired by the Accelerating Medicines Partnership (AMP) model.(1)

Collaborative Research in Inflammatory Arthritis: Lessons from AMP

Professor Vivian Bykerk presented a key-note talk that described AMP,(1) its successes, and the lessons learned over the past 4 years. AMP has been a platform for clinical, translational, and implementational science that was created to find solutions for important clinical-practice challenges in systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), type II diabetes, and Alzheimer's disease. AMP has worked closely with research groups in the United Kingdom and the European Synovitis Study Group to enable ultrasound-guided synovial tissue biopsies from rheumatoid joints. These technologies are cutting edge and include robust high-resolution sequencing and transcriptomic profiling at the single cell level.(1, 2) The introduction of these new technologies has brought new skills and expertise to the contributing centres, which will be valuable for research projects outside of AMP.

Professor Bykerk briefly described the past 4 years of the AMP process. In the first year, the initial request for applications for proposals related to rheumatologic diseases was made for sites that could provide studies or technologies to advance precision medicine in RA and SLE. There were 5 sites selected for RA and 5 sites selected for SLE. Collaborators trained health care providers to perform ultrasound-guided synovial biopsies at these sites. The SLE studies focused on the analysis of renal biopsies.

In the second year, the group created a network study, which was a milestone-driven exploratory period for the development and validation of SOPs and protocols with 3 key phases: SOP development, the implementation of pipeline analytics that compared RA with osteoarthritis, and the development of an observational study of RA. AMP is structured with the following 10 committees: (1) executive; (2) steering; (3) national leadership committee ((NLC) reporting to the steering committee); (4) disease focus group for RA and SLE ((DFG) reporting to the NLC); (5) clinical study group; (6) technology; (7) tissue group; (8) policy; (9) operations; and (10) fibroblast, monocyte, T-cell, and B-cell group. Committees were designed to be small to permit timely decisions, and the National Institute of Health (NIH) provides overarching administration. Each AMP centre has a principal investigator (PI) who sits on the NLC and has 1 vote (not all PIs are on the steering committee).

Methods to devise, validate, and establish SOPs for tissue sampling, processing, and analysis were described. Pipeline analytics have included the use of CyTOF, bulk RNA-sequencing, single-cell RNA sequencing, multi-parameter flow cytometry, and histomorphic studies that use pathway analysis. Nested studies have permitted the exploration of novel techniques such as tetramer-based sorting of antigen-specific lymphocyte, T and B cell receptor sequencing, and single-cell laser-capture microscopy. It was emphasised that expertise in systems biology analysis has been extremely important. New techniques have also been developed, including: Dropseq, which is used to sequence arthroplasty tissue at the bedside;(2) 10X-genomics; and CITE-seq, which permits the cellular indexing of transcriptome and epitopes by sequencing, thus combining the identification of single-cell transcriptomes and protein markers at the single-cell level.(3)

AMP is now entering phase 2, an observational study of patients with active RA (clinical disease activity index >10) derived from 1 of 3 groups: DMARD-naïve or minimally-exposed, methotrexate inadequate responder at week 12, and TNFi inadequate responders. Ultrasound-guided synovial biopsies have been taken in 48 patients (knee 40%, wrist 42%, ankle 10%, MCPJ 8%, and other sites) across 20 trained-centres. In phase 2, 150 subjects are being sought, with 20 having repeat biopsies.

Funding of USD 3 million was secured to establish the cohort, to clinical phenotype, and to perform biopsies. A further USD 3 million was secured to perform the analyses. Funding has been derived primarily (40%) from the pharmaceutical industry (AbbVie, Bristol Myers Squibb, Merck, Pfizer, Sanofi, and Takeda), followed by the Foundation for the National Institutes of Health (FNIH) (40%) and other non-profit organisations (10-20%; e.g., Arthritis Foundation, Alliance for Lupus Research, and the Rheumatology Research Council).

The AMP group initially met very frequently to gain consensus on strategic plans. It continues to meet regularly to update contributors on progress, to draft publications, and to enthuse researchers. Operationally, all synovial biopsy samples are transported to 1 centre for analysis. The nested studies were designed to be longitudinal, rather than cross-sectional, to improve the generalisability of the results. Deciding on the SOP was mostly determined by the study question being posed. Of note, no issues were encountered in transferring biopsy samples between the United States and the United Kingdom. Clinical data is entered into an online database (REDCap) and supervised by Stanford University, but, as with all studies, some missing data remain a challenge. AMP has inspired groups of independent investigators to work more closely as part of a consortium.

CRN Pilot Study 1: PsA-BioDAM

Dr. Vinod Chandran acted as a convener to propose a PsA-Biomarkers for Joint Damage (BioDAM)-related CRN pilot study. Dr. Chandran was supported by Dr. Walter Maksymowych, Professor Oliver FitzGerald, Dr. Philip Mease, Heidi Bertheusen (PRP), Maarten de Wit (PRP), and David Collier (Amgen).

Given that PsA is a heterogeneous disease with erosions evident in 47% of cases by 2 years, there is a need to identify biomarkers to help stratify treatment and identify changes in disease activity with treatment. Known clinical prognostic markers include polyarticular disease, dactylitis, high acute phase response, and delayed presentation to specialist rheumatology care. Joint erosions and damage are markers of severe disease and have previously been demonstrated to be associated with poorer functional status, higher economic impact, and a risk factor for mortality.

The PsA-BioDAM project was developed with the primary objective to determine the independent predictive ability of serum biomarkers for joint damage. Candidate biomarkers include: collagen proteins, serum calgranulin (S100A8/S100A9), macrophage colony stimulating factor (M-CSF), receptor activator of nuclear factor kappa-B ligand ((RANKL) but not Dickopff-1), vascular endothelial growth factor (VEGF), angiopoietin-2, and serum amyloid A. Advanced discussions have taken place between GRAPPA and Amgen on utilising the SEAM study (phase III, 48-week study comparing etanercept and methotrexate as mono- and combination-therapy in subjects with PsA; radiographs performed at 6 and 12 months; serum sampled at baseline and 8, 24, and 48 weeks) biosamples as part of this PsA-BioDAM-related CRN pilot study.

A leading hypothesis is that surrogate biomarkers will predict which patients are at risk for peripheral radiographic damage in PsA. The aim of the study will be to identify biomarkers that predict joint damage with the goal to stratify treatment in the early stages and limit bone resorption and cartilage degradation. The primary study objective will be to determine the independent predictive validity of several biomarkers in predicting structural damage (erosions) in PsA patients who receive methotrexate, etanercept, or both. An aliquot of each serum sample with the linked clinical and radiographic data will be provided to GRAPPA. A panel of over 200 candidate protein biomarkers will be tested on the serum samples that are provided using optimised multiple reaction monitoring (MRM) assays and testing for metalloproteinase inhibitor 1, alpha-1-acid glycoprotein 2, serotransferrin, platelet glycoprotein Ib alpha chain, di-N-acetyl chitobiase, gelsolin, fibroblast growth factor receptor

1, leukocyte immunoglobulin-like receptor subfamily B member 2, C-X-C motif chemokine 13, ADP-ribosyl cyclase 2, complement component C7, haptoglobin-related protein, apolipoprotein E, apolipoprotein D, GTPase KRAS, complement factor B, tumor necrosis factor α, SPARC, C-X-C motif chemokine 10, alpha-1-antichymotrypsin, and tyrosine-protein phosphatase non-receptor type 2. It is anticipated that a panel of markers with baseline or change values will be predictive. Discussions are in progress to determine who should perform the analyses: academics, industry scientists, or a combined effort. It was emphasised that the PsA-BioDAM study aims to identify serum biomarkers that predict radiographic damage that are independent of CRP in order to add value to known biomarkers.

The model agreement is now also being discussed with Lilly (SPIRIT-P1 and P2 studies), Pfizer (OPAL Broaden and Beyond studies), AbbVie (Upadacitinib studies), and Bristol-Myers-Squibb (986165 TYK2i studies) as providers of serum samples, which will enable this study to be a low-risk, lower-cost pilot for the CRN.

CRN Pilot Study 2: Predicting the Development of PsA Among Patients with Psoriasis

Drs. April Armstrong and Alexis Ogdie co-led the proposal for another CRN pilot study related to predicting the development of PsA among patients with psoriasis only (PsC). Drs. Armstrong and Ogdie were supported by Professors Christopher Ritchlin, Dafna Gladman, Steve Pennington, Philip Helliwell, and Cheryl Rosen, and Drs. Carmel Stober, Jose Scher, Souyma Chakravaty (Janssen), Jaci Anderson (Abbvie), John Latella (PRP), Jeffrey Chau (PRP), and Rodrigo Firmino (PRP).

Dr. Stober described how the evidence to date suggests that the progression of PsC to PsA is determined by the complex interplay of genes, microbiome, immune system, environment, and other exposures. In RA, it has been demonstrated that genes in the MHC region, as well as PTPN22, PADI4, and CTLA-4 contribute to genetic susceptibility for RA. Genome wide association studies indicate that genetics account for 36-65% of RA

heritability, with the shared epitope being a major contributor.(4) Several transcriptome and proteomic studies have identified differential expression of RNA and proteins in RA.(5)

Dr. Ogdie gave an epidemiological perspective on the varied types of evidence in literature, including associations (from cross-sectional or case-control studies), etiologic risk factors (which have a temporal association that occurs before the disease has begun and that may lead to the progression of PsC to PsA), and predictors including PsC factors that might identify which patients are likely to identify PsA but may or may not be a part of the causal pathway, as shown in Figure 1. Subclinical changes in the entheses and joints have been investigated in PsC cases using ultrasound, MRI, PET-CT, and micro-CT imaging to ascertain if they predict progression to PsA. However, there is limited prospective data and results are heterogenous.(6, 7) Ongoing work will aim to define these earlier stages of disease.

Dr. Rosen gave an overview of the University of Toronto Psoriasis Cohort, a cohort of patients with PsC who have been followed at least yearly since 2006 in order to identify factors associated with the development of PsA. At 8 years of follow-up, 51 of 464 enrolled PsC cases had developed PsA, which equates to an annual incidence rate of 2.7 cases per 100 patients. Severe psoriasis, psoriatic nail pitting, uveitis, and a family history of PsA(8) were associated with an increased risk of developing PsA. The risk of new onset PsA remained the same and did not lessen over time. Of note, there appears to be a phase prior to the diagnosis of PsA of increased non-specific musculoskeletal symptoms.(8) In other studies, obesity has been demonstrated to be a risk factor for the progression of PsC to PsA(9, 10) but in some respects is a confounder, particularly in the relationship between psoriasis severity and the development of PsA. Another unique “predictor” that was discussed is smoking. In the Toronto cohort, 1 study found current smoking was associated with a decreased likelihood of developing PsA. However, because smoking is also associated with the development of PsC, this may be a misleading finding because, when compared to the general population, smoking is either not associated with the development of PsA or is positively associated. Thus, comparing potential risk factors between

populations with PsC and PsA, rather than comparing populations with PsA and controls (particularly when the factor may trigger the development of PsC), may cause spurious results. It is therefore important to be aware of collider stratification bias.(11)

Drs. Scher and Pennington described the pathophysiology, varying phenotypes, and candidate biomarkers of PsC progressing to PsA. They emphasized that the onset of PsA should not be considered in a dichotomous manner but rather as a spectrum of increasing manifestations. In some respects, clinicians and researchers create arbitrary thresholds for when a diagnosis of PsA is justified, and this pitfall should be avoided in order to identify a biomarker of PsC progressing to PsA. A variety of other approaches were proposed, including leveraging skin phenotypes as biomarkers and considering different biomarkers for transition into various domains. It was debated whether the PsA research community is in a position to generate SOPs for extraction and processing on different platforms, as well as whether data from various processing centres can be combined. The need for "Big Data" analysis methods to manage this was again emphasized.

Dr. FitzGerald described how HLA genotype modulates disease expression in PsA, the need for dense genotyping of immune-related susceptibility loci, and the emerging and compelling evidence for the existence of PsA-specific risk loci.(12) Of note, HLA-B27 is the only validated biomarker of PsC progression to PsA. Some oncology researchers are moving away from genomics and using RNA-sequencing and proteomics to identify biomarkers in similar contexts. There were 3 key discussion items debated, including:

(1) whether susceptibility loci identified as being specific for PsA are sufficiently sensitive and/or specific to discriminate those who may develop PsA from those with PsC;

(2) whether the current PsC cohorts (e.g., Toronto, Frankfurt, United Kingdom, and Dublin) are large enough to test the ability of PsA-specific loci and whether they are collecting appropriate clinical data, imaging, and biosamples; and

(3) whether future studies should include the genome-wide investigation of transcription factors in CD8+ memory T cells in both PsA and PsC.

CRN Pilot Study 3: Biomarkers Predicting Treatment Response in PsA and PsC

Professor Oliver FitzGerald convened the third pilot study and was supported by Professors Dafna Gladman and Philip Mease, and Drs. Deepak Jadon, Kristina Callis Duffin, Stefan Siebert, Conor Magee, Niti Goel, and Denis O'Sullivan (PRP), Shelly Kafka (Janssen), Lara Fallon (Pfizer), and Maureen Kelly (AbbVie).

Drs. Mease and O'Sullivan introduced the major unmet need for biomarkers to predict treatment response in PsA and PsC. They discussed how lessons can be learned from oncology where disease management is now molecularly guided to treatments that are less likely to be toxic and more likely to be efficacious, which will ultimately improve clinical outcomes. This "personalised" and "precise" approach, which is tailored to the individual patient's genetic, epigenetic, cellular, and/or molecular phenotype, is needed in psoriatic disease management. In some respects, the current treatment paradigm in psoriatic disease is comprised of: (1) stepwise treatment that starts with lower cost, potentially less toxic but also potentially less effective medicines; (2) "trial and error" treatment choices that often start with methotrexate and then possibly add or substitute with another conventional synthetic disease-modifying antirheumatic drugs (csDMARD); and (3) treatment that tries 1 or 2 anti-TNF therapies. These are often followed by treatment with antagonise interleukin (IL)-17, IL-12/23, phosphodiesterase 4, or janus kinase (JAK) without much information to guide that decision.

While imprecise choices may not be fatal, as in oncology, uncontrolled symptoms, progressive structural damage, work loss and disability, toxicity, and treatment expense all represent a "cost" to the patient, the patient's family, and society. A precision medicine approach in psoriatic disease may lead to rational step-wise and/or combination therapy; quicker achievement and maintenance of treat-to-target goals of remission or low disease activity; better prediction of adverse effect profile; reduced cost in terms of toxicity, structural damage, work productivity, and economics; and "guided treatment regimes" of induction,

maintenance, tapering, or withdrawal. Miyagawa, et al have recently demonstrated that response to TNFi, IL-17i, and IL-12/23i therapies in PsA can be associated with the relative abundance of Th1 and Th17 cells in the peripheral blood as detected by flow cytometry-based immunophenotyping.(13)

Drs. Magee and Jadon presented preliminary results of their systematic literature review (SLR) on biomarker (genetic, serum, cellular, urine, synovial, and skin biopsy) predictors of treatment response in PsA and PsC. Of 558 articles retrieved, 31 met eligibility criteria: 11 in PsA and 20 in PsC. In PsA, 3 studies examined synovium, 1 examined genetic polymorphism, and 7 examined serum proteins. In PsC, 8 studies examined genetic polymorphisms, 2 examined skin biopsies, and 10 examined serum or plasma proteins or antibody levels. There was much heterogeneity in study designs, biosampling methods, analysis techniques, and clinical outcome measures. Meta-analysis was therefore not possible. Of note, few biomarkers were tested in independent cohorts, and there are, therefore, no validated or even strong candidate biomarkers of treatment response in either PsA or PsC. The full SLR will be reported in due course.

Dr. Jadon described ongoing but unpublished research on this theme. The Dublin Measuring Outcome in Psoriatic Arthritis (MOPsA) group (led by Dr. Oliver FitzGerald) is analysing the Tight Control Works in Psoriatic Arthritis (TICOPA) cohort (led by Drs. Philip Helliwell and Laura Coates) (n=82 baseline PsA samples) to identify proteins that predict achieving minimal disease activity (MDA). In addition, PsA samples from Amsterdam from patients of Drs. Leonieke van Mens and Dominique Baeten, who are starting golimumab or methotrexate are undergoing MRM assay to test for predictors of treatment response. A trial within cohort study (MONITOR) of 3 centres in the United Kingdom (led by Drs. Laura Coates, Deepak Jadon, and William Tillett) is now recruiting to an inception cohort of PsA patients (n=500) followed for 5 years, with whole blood (cellular, DNA, RNA, serum), urine, and stool collected at first presentation and 3, 6, 9, 12, 18, 24, 36, 48, and 60 months. Patients will be treated as standard practice with csDMARDs, biologic disease-modifying antirheumatic drugs (bDMARDs), and targeted synthetic disease-modifying antirheumatic

drugs (tsDMARDs). Predictors of treatment response will be 1 of several study end-points. Dr. Stefan Seibert and Professor Iain McInnes in Glasgow are assessing several biomarkers of therapy from RA in PsA patients to determine generic biomarkers of response, rather than drug- or disease-specific biomarkers, as part of the ScOttish Psoriatic arthritis Observational Study (SOPHOS) and BASSPA study. Psoriatic Arthritis Research Consortium (PARC) is a 4-centre collaboration on the east coast of the United States (led by Drs. Ogdie, Scher, Reddy, and Walsh) that is longitudinally collecting clinical, imaging, and biosamples in PsA cases.

Professors Oliver FitzGerald and Dafna Gladman presented how this pilot may be taken forward with GRAPPA alone or through collaboration with industry partners. Considerations for a collaborative project with industry might include: working with 1 or more companies that have conducted randomised controlled trials (RCT) with detailed baseline and follow-up measures that have stored biosamples (e.g., serum) that are then made available to GRAPPA researchers. An initial "discovery" type study where patients who clearly respond to the study drug (either MDA or remission criteria) are compared with patients who fail to meet primary outcome measure (e.g., American College of Rheumatology 20% response criteria) or who get worse. Baseline samples (n= 10-20 per group) could be subjected to analysis using several platforms such as mass spectrometry-based protein analysis, SOMAscan, and Multiplex Luminex transcriptomics that look for individual or groups of markers that distinguish responders from non-responders at baseline. The funding for such a study is not likely to be prohibitively expensive.

It was therefore proposed that 5 centres with a track record of clinical research, biosample collection, and biosample storage be identified. Then, 8 patients per centre with active PsC and PsA who require treatment intervention (standard RCT entry criteria) are enrolled in an open-label study with an agreed therapy, likely starting with a TNFi, over a period of 6 months. Standard clinical data would be collected in an agreed database (likely REDCap) at baseline, and 3 and 6 months. Patients would be defined as responders if they meet either MDA or remission criteria, and non-responders would be defined as those who

fail to meet the primary outcome measure of ACR20 or those who clinically deteriorate. The estimated number of responders, predicting that 25% reach MDA, is 10. The estimated number of non-responders, assuming a 30% non-response rate, is 12. Biosamples (e.g., blood, PBMC, DNA, RNA, and possibly tissue) would be collected and stored at defined intervals using agreed SOPs, transported to the iPART group, and then analysed in 1 centre using validated laboratory techniques. The baseline samples (discovery) could be subjected to analysis using several platforms that look for individual or groups of baseline markers that separate responders from non-responders, such as LCMS, SOMA scan, Multiplex Luminex Elisa, and Transcriptomics. Identified biomarkers could be validated in all patients using assays such as MRM.

There are a number of advantages to such an approach. First, a small study would allow for clinical protocols to be developed by the CRN, which would operate across centres. Second, such an approach would allow for the development of SOPs for the collection, storage, and transport of biosamples across international borders. Third, this approach would ultimately provide evidence of the CRN's value and ability to share the clinical database and sample collection SOPs with all centres that would like to collaborate and contribute.

Based on costs for similar clinical studies, it is estimated that the cost per patient enrolled would be CAD 4,800. With the required 40 patients enrolled, the total cost would be CAD 192,000. This would include costs for database development and agreement; SOP development and agreement; and discovery and validation costs based upon samples being collected, stored, transported, and analysed for 40 patients at 3 timepoints.

The next steps and timelines for this pilot are to: (1) complete and publish the SLR (Quarter 4 of 2018); (2) complete contracts with industry partners regarding the sharing of samples, funding, and work-plan (Q4 2018); (3) identify industry partner(s) for assistance with pilot study development (Q1 2019); (4) prepare a detailed study proposal, including the development of a database, the standardisation of SOPs, and the development of ethics proposals (Q2 2019); and (5) identify 5 lead contributing centres (Q3 2019).

Discussion

Prior to the 2018 GRAPPA annual meeting, the attendees were asked to review a draft of the "GRAPPA-CRN Strategic Plan". The entire GRAPPA membership then participated in 8 workshops at the annual meeting that were facilitated by members of the CRN steering committee. The draft strategic plan was amended based on comments received at the workshops and discussions at the subsequent CRN symposia. The final strategic plan for implementation is presented in Tables 1-5. Table 1 includes the executive summary and "elevator pitch" for the CRN. Table 2 describes the CRN's mission, vision, and goals and how these align with GRAPPA's broader mission. Table 3 details the CRN's strengths, weaknesses, opportunities, and threats (SWOT) analysis. Table 4 identifies the target stakeholders, landscape, and competition analysis. Finally, Table 5 details a 5-phase plan, key team members, operational plan, financial projections, and implementation plan.

Conclusions

The CRN meeting provided an opportunity to identify 3 pilot projects, to discuss gaps in current knowledge of these themes, and to devise a research plan to address them. GRAPPA members heard from an expert from a similar large research consortium, which prompted the CRN to commence detailed planning of the 3 pilot research projects and their funding mechanisms.

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