Principal Investigator

First Name: José
Last Name: da Silva
Degree: PhD
Primary Affiliation: Centro Hospitalar e Universitário de Coimbra
E-mail: jdasilva@ci.uc.pt
Phone number: 00351917568433
Address: Serviço de Reumatologia, piso 7
Praceta Prof. Mota Pinto
City: Coimbra
State or Province: Coimbra
Zip or Postal Code: 3000-075
Country: Portugal
SCOPUS ID: 7201732846

2017-1451

General Information

Key Personnel (in addition to PI): **First Name:** Ricardo
Last name: Ferreira
Degree: PhD student
Primary Affiliation: Rheumatology department, Centro Hospitalar e Universitário de Coimbra, Coimbra, Portugal
SCOPUS ID: 56985168400

First Name: Pedro
Last name: Machado
Degree: PhD
Primary Affiliation: Centre for Rheumatology & MRC Centre for Neuromuscular Diseases, University College London, London, UK
SCOPUS ID: 35243075300

First Name: Laure
Last name: Gossec
Degree: PhD
Primary Affiliation: Faculty of Medicine, UPMC University Paris 06, GRC-UPMC 08 (EEMOIS), Paris, France
SCOPUS ID: 6602254276

First Name: Cátia
Last name: Duarte
Degree: PhD student
Primary Affiliation: Rheumatology department, Centro Hospitalar e Universitário de Coimbra, Coimbra, Portugal
SCOPUS ID: 22134319900

First Name: Eduardo
Last name: Santos
Degree: PhD student

Primary Affiliation: Emergency department, Centro Hospitalar e Universitário de Coimbra, Coimbra, Portugal
SCOPUS ID: 57191188153

First Name: Mwidimi
Last name: Ndosi
Degree: PhD
Primary Affiliation: University of the West of England, Bristol, UK
SCOPUS ID: 25960281200

First Name: Désirée
Last name: van der Heijde
Degree: PhD
Primary Affiliation: Leiden University Medical Centre, Leiden, The Netherlands
SCOPUS ID: 35380236300

Are external grants or funds being used to support this research?: No external grants or funds are being used to support this research.
How did you learn about the YODA Project?: Data Holder (Company)

disclosure_rf2.pdf

yoda_disclosure_pm_-_signed.pdf

yoda_form_signed_lg.pdf

yoda_es.pdf

yoda_disclosure_mn.pdf

yoda_disclosure_cd.pdf

yoda_disclosures_dvdh.pdf

yoda_disclosure_japs.pdf

Certification

Certification: All information is complete; I (PI) am responsible for the research; data will not be used to support litigious/commercial aims.
Data Use Agreement Training: As the Principal Investigator of this study, I certify that I have completed the YODA Project Data Use Agreement Training

Associated Trial(s): NCT00264537 - A Multicenter, Randomized, Double-blind, Placebo-controlled Trial of Golimumab, a Fully Human Anti-TNFa Monoclonal Antibody, Administered Subcutaneously, in Methotrexate-naïve Subjects with Active Rheumatoid Arthritis
NCT00264550 - A Multicenter, Randomized, Double-blind, Placebo-controlled Trial of Golimumab, a Fully Human Anti-TNFa Monoclonal Antibody, Administered Subcutaneously, in Subjects with Active Rheumatoid Arthritis Despite Methotrexate Therapy
NCT00269867 - A Placebo-Controlled, Double-Blinded, Randomized Clinical Trial of Anti-TNF Chimeric Monoclonal Antibody (cA2) in Patients With Active Rheumatoid Arthritis Despite Methotrexate Treatment
NCT00973479 - A Multicenter, Randomized, Double-blind, Placebo-controlled Trial of Golimumab, an Anti-TNFalpha Monoclonal Antibody, Administered Intravenously, in Patients With Active Rheumatoid Arthritis Despite Methotrexate Therapy
What type of data are you looking for?: Individual Participant-Level Data, which includes Full CSR and all supporting documentation

Research Proposal

Project Title

Long-term Impact of Patient Global Assessment on radiographic damage and physical function in patients with RA in Remission vs "near-remission"

Narrative Summary:
Remission is the recognized target for treatment of rheumatoid arthritis (RA). When remission is not reached an increase/change in immunosuppressive therapy is required. Remission is defined by the number of tender and swollen joints, by a inflammatory parameter and by a patient reported outcome: the patient global assessment (PGA). It has been discussed if the inflammatory activity of the disease should be assessed separated from the disease impact perceived by the patient. The primary aim of this study is to compare two different definitions of disease remission (including or excluding PGA) regarding the prediction of long-term radiographic damage and physical function in patients with RA.

Scientific Abstract:
Background: Remission is the recognized target for treatment of rheumatoid arthritis (RA). The current definition of remission[1] includes only one patient reported outcome (PRO), the patient global assessment (PGA). PGA proved to be crucial to decide whether a patient has attained remission (target) or needs reinforced therapy. This study is designed to clarify whether PGA should be/not included in this definition.
Objective: The primary aim of this study is to compare two definitions of disease remission (including or excluding PGA) regarding the prediction of long-term radiographic damage and physical function.
Study design: Meta-analysis of individual patient data.
Participants: Patients with RA included in extensions of randomized controlled trials of biological agents.
Main Outcome measures: Percentage of individuals with i) a good radiographic outcome (change ?0 in radiographic scores), and ii) a good function outcome (HAQ with change ?0 and consistently ?0.5) during the second year of the trial.
Statistical analysis: Positive likelihood ratios for good outcomes will be compared for the two definitions of remission: 1) ACR/EULAR Boolean definition [tender (TJC28) and swollen joint counts (SJC28) are both ?1, C-reactive protein (CRP) ?1, and PGA ?1]; 2) Near-remission (TJC28, SJC28, and CRP all ?1 and PGA>1). In order to take into consideration the time variable and to adjust for important covariates (e.g. gender, age and disease duration at baseline, radiographic damage at baseline, treatment arm), binomial Generalised Estimating Equations will be used.

Brief Project Background and Statement of Project Significance:
Disease remission or low disease activity is now a realistic therapeutic target in every patient with RA.[2, 3] To assess it, the American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR) proposed a Boolean definition of remission,[1] which requires that TJC28, SJC28, CRP (in mg/dl), and PGA (0–10) are all ?1. This was elected as the preferred definition to use in daily care of RA.[3]
PGA is the sole PRO included in the currently accepted definitions of treatment target,[1-3] justified by its responsiveness to treatment in clinical trials.[4] However, several studies[5-14] have shown that PGA is not solely influenced by RA disease activity, but also by sociodemographic features, geographic area, cultural and ethnic aspects, psychological factors, comorbidities and fibromyalgia, among others.
Patients that fail only PGA out of the 4 Boolean criteria have been called as in "near-remission".[15] The proportion of patients in near-remission could vary from 6.5%[15] to 38.2%,[14] which can represent up to four times the proportion of patients in remission.[5, 14-18] Following current treatment guidelines[2, 3] this state of near-remission would justify intensification of immunosuppressive treatment pending patient's agreement, structural damage, comorbidities or contraindications.[3]
The importance of incorporating PROs in the decision process is indisputable. The issue is whether PGA conveys information that should be taken into account when considering changing immunosuppressive regimens in patients that have otherwise achieved a remission state.
Progression of joint damage is one of the most important outcome measures in RA.[19] A recent systematic literature review[20] investigated the clinical predictors of radiographic progression in RA, including disease activity indices and their individual components. Regarding the individual components, only SJC and acute phase reactants were associated with radiographic progression. Published data on PGA was limited and did not support its use as unique tool to predict progression of joint damage.[20] Four studies (2 RCTs and 2 prospective cohorts) were included in this review, with 1 to 3 years of follow-up. Most of studies included tested synthetic DMARDs, but radiographic progression may differ in patients receiving biologic therapy. A subsequent observational study[21]

(n=527, early RA, follow-up= 8 years) demonstrated that 31% of patients in sustained ACR/EULAR Boolean remission had radiographic progression. There was no significant contribution of PGA to the likelihood ratio of the this outcome.[21]

These observations suggest that the concept of "Disease remission" should probably not include PGA for the purposes of: i) guiding immunosuppressive therapy and, ii) assessing the efficacy of medication, including bDMARDs. Such a definition of remission, i.e. excluding PGA, might be designated as "3v-remission".

This study will test the hypothesis that the 3v and 4v-remission are associated with equal prevention of structural damage. If this is demonstrated 3v-remission should be adopted as the target for immunosuppressive therapy.

Specific Aims of the Project:

The primary aim for this study is to compare the long-term (2 years after baseline) progression of radiographic damage between patients with RA who reach "4v-remission", "4v near-remission" ("3v-remission") and "Non-remission".

The main hypothesis to test is that the 3v and 4v-remission are associated with equal prevention of structural damage.

Secondary aims will compare physical function outcome and the combination of radiographic damage and physical function outcomes across the same definitions at the same endpoint (second year after baseline). If data is available, secondary end-points for these three outcomes will include stability between 1 and 5 years and between 1 and 10 years after baseline.

We also aim to explore if these comparisons are influenced by important covariates (gender, age at baseline, disease duration at baseline, Rheumatoid Factor (RF), Anti-Citrullinated Peptide Antibody (anti-ACPA), radiographic damage at baseline, treatment arm).

What is the purpose of the analysis being proposed? Please select all that apply. Participant-level data meta-analysis

Participant-level data meta-analysis will pool data from YODA Project with other additional data sources

Research Methods

Data Source and Inclusion/Exclusion Criteria to be used to define the patient sample for your study:

Type of studies

This study will include published RCTs, including long-term extensions, which evaluate the efficacy of biologic Disease-modifying anti-rheumatic drugs (bDMARDs) on radiographic damage in patients with RA. Studies with less than two years of follow-up will be excluded as well as studies with less than 200 patients with 2-year follow-up. The complete list of trials requested to data owners can be found in Appendix 1 to this proposal.

Participants

Both men and women with diagnosis of RA, as defined by the criteria endorsed by ACR and EULAR[22, 23], will be included.

Types of interventions

Studies testing the efficacy of any bDMARDs [Tumor necrosis factor (TNF) inhibitors; Interleukin (IL) inhibitors; B-cells inhibitors; and T-cells inhibitors] will be studied. Both intravenous and subcutaneous administration will be included. Studies testing the efficacy of biological spacing or suspension will be excluded.

Types of baseline assessments

As a minimum, studies will need to have assessed the ACR/EULAR Boolean-based criteria (SJC28, TJC28, CRP, and PGA) at baseline and at 6 and 12 months and the radiographic damage assessment at baseline, 12 and 24 months.

Main Outcome Measure and how it will be categorized/defined for your study:

In this study we will adopt the definitions of good outcome in radiographic damage and function (separately and combined) adopted in the ACR/EULAR provisional definition of RA remission.[1]

1) Good radiographic outcome is defined as stable radiographic scores over 1 year (defined as change ?0 in Sharp [24] or modified Sharp scores[25-27] during the second year of the trial).

2) Good physical function outcome is defined as stable and low scores of Health Assessment Questionnaire (HAQ)[28] (change ?0 and HAQ score consistently ?0.5 during the second year of the trial).
3) Good radiographic outcome and good function as the combination of 1) and 2).

Thus, our main Outcome measures will be:
a) Percentage of individuals with a good radiographic outcome during the second year of the trial.
b) Percentage of individuals with a good function outcome during the second year of the trial.
c) Percentage of individuals with a good radiographic and good function outcome during the second year of the trial.

The combination of radiographic and function outcomes and changes ?0 are justified by the significant reduction in radiographic progression in RCTs with these drugs.[29]

Main Predictor/Independent Variable and how it will be categorized/defined for your study:
Analyses will be based on the definition of different remission states, as follows:
a) ACR/EULAR Boolean-based remission[1], also designed in this project as "4v-Remission" (i.e., TJC28?1, SJC28?1, CRP mg/dl?1, and PGA?1/10)
b) "4v-near-remission"[18, 30], defined as remission for all criteria (score?1) except PGA
c) "3v-Remission", defined as TJC28 ?1, SJC28 ?1, and CRP mg/dl ?1 (i.e. PGA is excluded from consideration). This concept brings together "4v-remission" and "4v-near-remission".
d) "Non-remission" defined as TJC28 or SJC28 or CRP mg/dl >1; this definition is the same regardless of considering 3 or 4 variables.

Individual patients will be attributed a given remission state group if that definition is achieved at both the 6 and the 12-months, following the definitions adopted by ACR/EULAR.[1] Patients whose classification differs at 6 and 12 months will be excluded if total numbers allow this option retaining sufficient statistical power. Otherwise they will incorporate a new group designated "transitional state". An exploratory analysis will be performed to consider all time points available and not only the 6 and 12-months visits (more details in statistics).

Other Variables of Interest that will be used in your analysis and how they will be categorized/defined for your study:
Other variables important for this study are:

- Patient characteristics (all at baseline only)
o gender
o age at baseline

- Disease characteristics (all at baseline only)
o disease duration at baseline
o RF
o ACPA
o Treatment arm

- Trial/visit information
o anonymised patient ID code (at baseline only)
o visit number or sequence
o visit date

Statistical Analysis Plan:
Sample size calculations
To determine the minimal sample size required to this study we used the formula proposed by Hajian-Tilaki[31] to compare two independent proportions regarding sensitivity and/or specificity of two test of unpaired design. Assuming 95% confidence and 80% power to detect a difference of 7% from a specificity of 98% (i.e. P1=98% and P2=91%) based on the results of a previous study,[21] it would be required a n=165 for each group (i.e., 165 patients in 4v-remission and 165 in 3v-remission). If assuming a more strict difference of 5% and specificities of P1=95% and P2=90%, the sample required will be n=433 for each group. Considering 15% as the average remission rate in clinical trials assessed by ACR/EULAR Boolean-based definition, the total number of patients required for pooled analysis is n=2887.
Data analysis

Analysis of IPD will need to be done separately, in secure platforms as request of data holders. All significance tests will be two tailed and conducted at 0.05 significance level. R software will be used within the platforms and STATA for other analysis. Missing data will not be submitted to any method of data imputation.

The first step will be the determination of number of true positive (TP), true negative (TN), false negative (FN) and false positive (FP) statistics. Then, sensitivity, specificity, positive and negative predictive value (PPV and NPV) will be determined for the ability of sustained remission (by 3v and 4v-remission) to predict good radiographic outcome. The positive likelihood ratios (LR+) will then be calculated by the formula: sensitivity/(1-specificity). All analyses will be repeated for secondary outcomes. To rank LR+ for 3v and for 4v-remission groups chi-square analysis using logistic regression will be used.

Measures to adjust for confounders

In order to take into consideration the time variable (i.e. the evolution within individual between visits), and to adjust for important covariates (mentioned above) binomial Generalised Estimating Equations (bGEE) will be used, considering all visit time points common to the included trials. This will provide an Odd Ratio (OR) for 3v and 4v-remission groups.

Sensitivity analyses

Although it has been shown that TNF inhibitor monotherapy had similar results to MTX monotherapy in terms of radiographic damage[32] we will perform a sensitivity analysis considering the different treatment arms (i.e. bDMARD monotherapy, cDMARD monotheraphy and combined therapy).

The number of years of follow-up could also affect the results of radiographic outcomes.[21] Thus, in addition to the main analysis of the 2-years outcome (the most frequently reported) we will assess outcomes also for 5 and 10-years after baseline.

Other factors that might influence radiographic progression are: patients with early versus established disease; patients naive to MTX or patients that failed MTX before bDMARD initiation. If the number of studies/patients allow, sensitivity analyses will be performed for these groups independently.

Data synthesis

The TP, TN, FN, and FP statistics obtained for each trial in the previous step will be used to synthetize the data. This will be performed using the command "midas" on Stata software.

To test heterogeneity among the studies, the I2 of Higgins and Thompson will be calculated.[33]

Exploratory analyses

The definition of "sustained" remission (and non-remission) based on only 2 time points (at 6 and 12 months) may not fully capture all relevant information.[34] Thus it will be described both the duration of remission (3v and 4v) as well as the interruptions in this desired state. It will be also explored whether the multiple remission and relapse periods are related to the long-term radiographic progression and compare the performance of 3v and 4v-remission definitions, using the "Continuity Reward" (ConRew) score and patient vector graphs proposed by Boers et al.[34]

Project Timeline:
Main milestones for this project are:
- Anticipated start of analysis: June-Sept. 2017
- Publication of PROSPERO brief protocol: June-Sept. 2017
- Publication of full protocol: June-Sept. 2017
- Analysis completion date: March 2018
- Preparation of first abstract for a major congress: April 2018
- Manuscript first draft: May 2018
- Manuscript first submitted for publication: June 2018
- Results reported back to the YODA Project: June 2018

Dissemination Plan:
We plan to publish a brief protocol of this study at PROSPERO registry, an International prospective register of systematic reviews (https://www.crd.york.ac.uk/PROSPERO/). A full protocol (which is already prepared and attached to this YODA project submission) will be submitted to "Systematic Reviews" journal as soon as we have a first authorization for IPD use from a data holder. This "holding" decision is just to prevent that it will be possible to do the analysis with data from RCTs, which we strongly believe that will happen.

The preliminary results of this project will be presented at "ACR 2018" and/or "EULAR 2019", the two major congresses in rheumatology. Depending on how much data we have access to, different presentations could be presented at both.

The final results will be submitted to "Annals of Rheumatic Diseases", the journal with highest impact in rheumatology (IF=12. 384). If not accepted we will try "Arthritis and Rheumatology" (IF=7.764), the 3rd highest ranked. The provisional definition of remission was published together by both of these journals.

Before manuscript submission to a journal or to a congress, companies will be asked to provide a critical appraisal of the draft manuscripts.

Bibliography:
1. Felson, D.T., et al., American College of Rheumatology/European League against Rheumatism provisional definition of remission in rheumatoid arthritis for clinical trials. Ann Rheum Dis, 2011. 70(3): p. 404-13.
2. Smolen, J.S., et al., Treating rheumatoid arthritis to target: 2014 update of the recommendations of an international task force. Annals of the Rheumatic Diseases, 2015. 75(1): p. 3-15.
3. Smolen, J.S., et al., EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2013 update. Ann Rheum Dis, 2014. 73(3): p. 492-509.
4. Jansen, J.P., et al., Comparative efficacy of biologics as monotherapy and in combination with methotrexate on patient reported outcomes (PROs) in rheumatoid arthritis patients with an inadequate response to conventional DMARDs--a systematic review and network meta-analysis. Health Qual Life Outcomes, 2014. 12: p. 102.
5. Vermeer, M., et al., The provisional ACR/EULAR definition of remission in RA: a comment on the patient global assessment criterion. Rheumatology (Oxford), 2012. 51(6): p. 1076-80.
6. Khan, N.A., et al., Determinants of discordance in patients' and physicians' rating of rheumatoid arthritis disease activity. Arthritis Care Res (Hoboken), 2012. 64(2): p. 206-14.
7. Ward, M.M., L.C. Guthrie, and M.I. Alba, Measures of arthritis activity associated with patient-reported improvement in rheumatoid arthritis when assessed prospectively versus retrospectively. Arthritis Care Res (Hoboken), 2015. 67(6): p. 776-81.
8. Egsmose, E.L. and O.R. Madsen, Interplay between patient global assessment, pain, and fatigue and influence of other clinical disease activity measures in patients with active rheumatoid arthritis. Clin Rheumatol, 2015. 34(7): p. 1187-94.
9. Sokka, T., et al., Disparities in rheumatoid arthritis disease activity according to gross domestic product in 25 countries in the QUEST-RA database. Ann Rheum Dis, 2009. 68(11): p. 1666-72.
10. Masri, K.R., et al., Validity and reliability problems with patient global as a component of the ACR/EULAR remission criteria as used in clinical practice. J Rheumatol, 2012. 39(6): p. 1139-45.
11. Studenic, P., et al., Discrepancies between patients and physicians in their perceptions of rheumatoid arthritis disease activity. Arthritis Rheum, 2012. 64(9): p. 2814-23.
12. Inanc, N., et al., The role of depression, anxiety, fatigue, and fibromyalgia on the evaluation of the remission status in patients with rheumatoid arthritis. J Rheumatol, 2014. 41(9): p. 1755-60.
13. Ferreira, R.J.O., et al., Suppressing inflammation in rheumatoid arthritis: Does patient global assessment blur the target? A practice–based call for a paradigm change. Submited.
14. Ferreira, R.J.O., et al., Drivers of patient global assessment in patients with rheumatoid arthritis who are close to remission: an analysis of 1588 patients. Submited.
15. Gossec, L., et al., Doctor, will my fatigue be better if I'm in remission? An exploratory analysis of 1284 Rheumatoid Arthritis (RA) patients indicates fatigue is the only aspect of patient-perceived impact to remain significant in ACR/EULAR boolean remission [abstract]. Arthritis Rheum, 2014. 66: p. S147-S148.
16. Gossec, L., et al., Does psychological status drive patient global assessment for rheumatoid arthritis patients who do not have any clinical signs of inflammation? An exploratory analysis of near-remission using the rheumatoid arthritis impact of disease (RAID) score. Annals of the Rheumatic Diseases, 2013. 72.
17. Balogh, E., et al., Comparison of remission criteria in a tumour necrosis factor inhibitor treated rheumatoid arthritis longitudinal cohort: patient global health is a confounder. Arthritis Res Ther, 2013. 15(6): p. R221.
18. Studenic, P., J.S. Smolen, and D. Aletaha, Near misses of ACR/EULAR criteria for remission: effects of patient global assessment in Boolean and index-based definitions. Ann Rheum Dis, 2012. 71(10): p. 1702-5.
19. Landewe, R. and D. van de Heijde, Is radiographic progression a realistic outcome measure in clinical trials with early inflammatory arthritis? Clin Exp Rheumatol, 2003. 21(5 Suppl 31): p. S37-41.
20. Navarro-Compan, V., et al., Relationship between disease activity indices and their individual components and radiographic progression in RA: a systematic literature review. Rheumatology (Oxford), 2015. 54(6): p. 994-1007.
21. Svensson, B., et al., Long-term sustained remission in a cohort study of patients with rheumatoid arthritis: choice of remission criteria. BMJ Open, 2013. 3(9): p. e003554.
22. Arnett, F.C., et al., The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. Arthritis Rheum, 1988. 31(3): p. 315-24.
23. Aletaha, D., et al., 2010 rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. Ann Rheum Dis, 2010. 69(9): p. 1580-8.
24. Sharp, J.T., et al., Methods of scoring the progression of radiologic changes in rheumatoid arthritis. Correlation of radiologic, clinical and laboratory abnormalities. Arthritis Rheum, 1971. 14(6): p. 706-20.
25. Ory, P.A., Interpreting radiographic data in rheumatoid arthritis. Annals of the Rheumatic Diseases, 2003. 62(7):

p. 597-604.

26. van der Heijde, D., How to read radiographs according to the Sharp/van der Heijde method. J Rheumatol, 2000. 27(1): p. 261-3.

27. van der Heijde, D.M., et al., Effects of hydroxychloroquine and sulphasalazine on progression of joint damage in rheumatoid arthritis. Lancet, 1989. 1(8646): p. 1036-8.

28. Fries, J.F., et al., Measurement of patient outcome in arthritis. Arthritis Rheum, 1980. 23(2): p. 137-45.

29. Landewe, R.B., et al., Is radiographic progression in modern rheumatoid arthritis trials still a robust outcome? Experience from tofacitinib clinical trials. Arthritis Res Ther, 2016. 18(1): p. 212.

30. Gossec, L., et al., Does psychological status drive patient global assessment for rheumatoid arthritis patients who do not have any clinical signs of inflammation? an exploratory analysis of near-remission using the rheumatoid arthritis impact of disease (RAID) score [abstract]. Annals of the Rheumatic Diseases, 2013. 72(Suppl 3): p. A393.

31. Hajian-Tilaki, K., Sample size estimation in diagnostic test studies of biomedical informatics. J Biomed Inform, 2014. 48: p. 193-204.

32. Aletaha, D. and J.S. Smolen, Joint damage in rheumatoid arthritis progresses in remission according to the Disease Activity Score in 28 joints and is driven by residual swollen joints. Arthritis Rheum, 2011. 63(12): p. 3702-11.

33. Moayyedi, P., Meta-analysis: Can we mix apples and oranges? Am J Gastroenterol, 2004. 99(12): p. 2297-301.

34. Boers, M., et al., A new graph and scoring system simplified analysis of changing states: disease remissions in a rheumatoid arthritis clinical trial. J Clin Epidemiol, 2010. 63(6): p. 633-7.

Supplementary Material: project_remission_3v_4v_20170316.pdf

appendix_1.docx