An eDElphi STudy to defINe and risk-stratify ImmunosupprESsion: Protocol for the DESTINIES Study

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Abstract

Background: There are considerable inconsistencies in how immunosuppression is characterised and subdivided as a clinical risk group. This is detrimental to both the precision and comparability of international disease surveillance efforts – negatively implicating immunosuppressed health outcomes. Clinical consensus must therefore be built around which conditions and medications would constitute immunosuppression, their gradations of severity, and how to formalise both in a definitive phenotype for ongoing use in surveillance data flows.

Objective: This protocol outlines e-Delphi objectives, methodology and statistical approaches that will help address this lack of consensus and construct an adult ‘immunosuppression’ phenotype.

Methods: Leveraging existing evidence for heterogeneous COVID-19 outcomes in immunosuppressed adults, this work will recruit between 10 and 50 clinical or policy experts in the remit of vaccine prioritisation. Subsequent to two rounds of clinical consensus building and one round of concluding debate, these panellists will suggest the conditions, dependencies and clinical coding languages that should be incorporated into a phenotype for ‘immunosuppression’ in adults. This work will be conducted iteratively, with opportunities for panellists to ask clarifying questions between rounds and provide ongoing feedback to improve questionnaire items. Statistical analysis will focus on levels of agreement between responses and rankings.

Results: This protocol outlines a robust method for generating consensus around best defining and subdividing adult immunosuppression for the benefit of disease surveillance.

Conclusions: A universally acceptable, clinically relevant, and computerised medical record compatible phenotype for adult immunosuppression will have immediate value for vaccine distribution and the prioritisation of scarce or expensive medical supplies amongst affected adults.

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Original Manuscript

An eDElphi STudy to defINe and risk-stratify ImmunosupprESsion: Protocol for the DESTINIES Study

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Abstract:

Background:

Globally, there are marked inconsistencies in how immunosuppression is characterised and subdivided as a clinical risk group. This is detrimental to the precision and comparability of disease surveillance efforts – both of which negatively implicate immunosuppressed care and their health outcomes. This was particularly apparent during the COVID-19 pandemic; despite collective motivation to protect these patients, conflicting clinical definitions created international rifts in how the immunosuppressed were monitored and managed during this period. We propose that international clinical consensus be built around the conditions that exhibit immunosuppression and their gradations of severity in relation to COVID-19. Such information can then be formalised into a digital phenotype to enhance disease surveillance and provide much-needed intelligence on risk-prioritising these patients.

Objective:

To demonstrate how Electronic Delphi (eDelphi) objectives, methodology and statistical approaches will help address this lack of consensus internationally and deliver a COVID-19 risk-stratified phenotype for ‘adult immunosuppression’.

Methods:

Leveraging existing evidence for heterogeneous COVID-19 outcomes in immunosuppressed adults, this work will recruit over 50 world-leading clinical, research or policy experts in the area of immunology and/or clinical risk prioritisation. Subsequent to two rounds of clinical consensus building and one round of concluding debate, these panellists will confirm the medical conditions that should be classed as immunosuppressed and their differential vulnerability to COVID-19. Consensus statements on the time and dose-dependencies of these risks will also be presented. This work will be conducted iteratively, with opportunities for panellists to ask clarifying questions between rounds and provide ongoing feedback to improve questionnaire items. Statistical analysis will focus on levels of agreement between responses.

Results:

This protocol outlines a robust method for improving consensus on the definition and meaningful subdivision of adult immunosuppression in relation to COVID-19.

Conclusions:

This protocol, if fully implemented, will deliver a universally acceptable, clinically relevant, and computerised medical record (CMR) compatible phenotype for adult immunosuppression. As well as having immediate value for COVID-19 resource prioritisation, this exercise and its output hold prospective value for clinical decision-making across all diseases that disproportionately affect the immunosuppressed.

Keywords: Immunosuppressed; immunocompromised; COVID-19; surveillance; phenotype

Introduction

At present, there is no clinical consensus around the conditions and medications that would confer immunosuppressed status upon an individual [1]. This population scales from 2% [2] to over 10% [3] of the general population dependent on the definition applied, most notably when diabetic, malnourished or elderly individuals are incorporated [3]. This disagreement on what constitutes ‘immunosuppression’ extends to how best to subdivide this heterogeneous population: out of the binary [4], continuum [5] and hierarchical [6] approaches available, there is currently no gold standard [7]. This inconsistency undermines ambitions for targeted care and disease surveillance as aggregate level analysis dominates and sub-trends lose visibility [7].

Despite this, it is well known that immunosuppressed patients experience worse infection outcomes [8] and, in some cases, respond poorly to vaccination [9]. Meanwhile, there has been no concerted effort to differentiate vaccine side effects within the immunosuppressed [10]. Without a clinically meaningful and computerised medical record (CMR) compatible means of identifying and subdividing immunosuppressed adults, it will not be possible to improve this poor resolution in vaccine benefit-risk profiling in this population. Clinical guidelines around vaccine dosing, scheduling, and boosting as well as policies on the targeted distribution of antivirals or passive forms of immunisation (monoclonal antibodies, convalescent plasma etc.) suffer as a result [7].

This study aims to obtain clinical consensus on a risk-stratified phenotype of adult 'immunosuppression' to be implemented within UK health databases as standard. The use of COVID-19 as our reference condition is justified by pandemic gains to the immunosuppressed literature base [11]. While findings of differential vulnerability for COVID-19 amongst immunosuppressed adults may not be fully generalisable to alternative infections or even paediatric patients, the specificity of COVID-19 immunosuppressed literature – inclusive of infection outcomes amongst extremely rare or complex diseases - enables comparisons across all conditions and medications cited by the *UK Immunisation Against Infectious Disease* manual [Green Book] [12, Appendix 1].

Methods

The objective of this protocol is to demonstrate how the Electronic Delphi (eDelphi) [13] study design will be used to surface a definitive and risk-stratified phenotype for adult immunosuppression based on vulnerability to COVID-19. This process will see panellists seek to align on the conditions to be included in said definition, their respective levels of risk for severe COVID-19 outcomes and key risk dependencies (time treated/ diagnosed/ in remissions and dosage of medication received etc.). Consensus will be determined by whether over ≥75% of panellists agree on definition contents and risk relationships. A range of consensus statements will also be presented and evaluated by this same ≥75% consensus target. These statements will assess panellist agreement on the heterogeneity of immunosuppressed patients and their COVID-19 infection outcomes as well as the accuracy of the draft phenotypes (multi-level and High vs Low Risk categorised) that will be presented between eDelphi rounds. The >75% consensus level is not arbitrary but based on systematic review of Delphi consensus definitions by Diamond and colleagues [14]; here, across a random sample of 100 successful Delphi investigations, 75% was the median threshold to establish consensus.

The Delphi Technique aims to build consensus on pre-specified topics by soliciting the opinions, testimonies, or judgments of experts (Delphi panellists) with successive, anonymised questionnaires [13]. This method is especially valuable for generating insight and informing decision-making on complex, sensitive, emerging, or under-researched subject matters [15]. Its anonymised nature reduces demand characteristics or the influence of dominant personalities that can both bias results in unblinded exercises [16]. Delphi questionnaires are improved upon by embedding opportunities for panellist feedback between consensus building rounds. The amount and type of questions presented, as well as the time available to reach consensus, determines the number of rounds attempted in each study.

The Electronic Delphi, or eDelphi, method hosts these investigations entirely online. This widens the pool for recruitment as geographical limitations are removed. Data management advantages and time and cost savings have also made the eDelphi method more attractive than in-person and paper-based alternatives [17].

Although neither Delphi nor eDelphi studies are supported by unambiguous methodological guidelines, the present protocol has cross referenced Conducting and Reporting Delphi Studies (CREDES) guidance [18] and recommendations from systematic reviews into successful Delphi

execution [14]. Its publication is intended to maximise study quality and transparency.

Study Management:

This study will be coordinated by the Clinical Informatics and Health Outcomes Research Group at the Nuffield Department of Primary Care Health Sciences, University of Oxford. Separate ethical approval was sought for this work but deemed unnecessary after review by both the University's dedicated Research Governance Ethics and Assurance Team and Joint Research Office Study Classification Group. It was determined that all activities fell under 'pre-research', 'priority setting' or 'survey'; as such, it would not be subject to the Department of Health's UK Policy Framework for Health and Social Care Research [19] and would not be subject to sponsorship or research ethics review. This decision was corroborated when cross-referenced with the Health Research Authority's dedicated review algorithm [20], attendant leaflet (*Defining Research* [21]*)* and Health Care Quality Improvement Partnership (HQIP) *Guide for Clinical Audit, Research and Service Review* [22].

A steering group comprised of senior staff members, a primary investigator, statistical supervisors, external research collaborators and an immunosuppressed patient champion will contribute to the design and implementation of the study protocol, provide ongoing advice during the study period, and assist in the interpretation, write-up, and dissemination of study results.

As illustrated in Figure 1, the study will involve a preparation period (to provide panellists with their consent form and pre-read materials), two rounds of consensus building and a concluding discussion group to field final comments, points of clarification, confirmation, dissent, and feedback from panellists. Subject to successful recruitment, the study will run between April and June 2024. Panellists will be given a two-week period to complete each round. To prevent attrition, reminders will be sent via email to non-responders at days 6, 10 and 12. As per recruitment, telephone calls will be made at day 10 to encourage form submission; this will only occur when this information is listed publicly or has been provided by panellists that consent to it being used for this purpose.

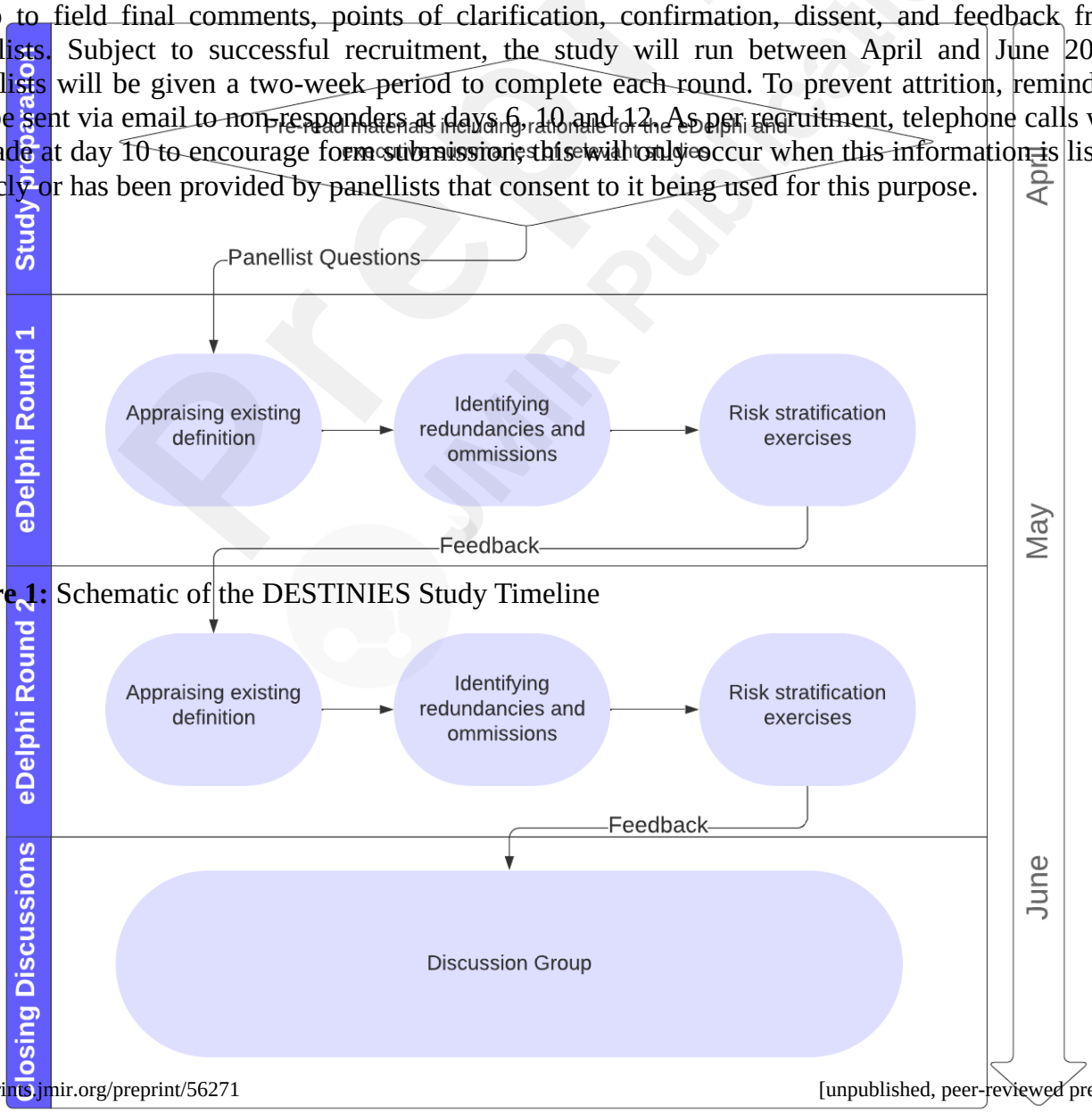

Figure 1: Schematic of the DESTINIES Study Timeline

Recruitment:

No sample size calculation is required for eDelphi methodology; however, at least 50 specialists will make up the international eDelphi panel. This is intended to ensure that both condition-specific and condition-general immunosuppressed experts are well-represented and to maximise the global footprint of this work. Panellists will not be paid for their participation but are made aware that due attribution will be given to any outputs of this work should they be willing to be named.
Panellists will be recruited based on their affiliation with the following:

- World Health Organisation (WHO) Global Advisory Committee on Vaccine Safety (GACVS)
- Coalition for Epidemic Preparedness Innovations (CEPI) Scientific Advisory Committee
- The Global Immunocompromised Health Coalition (GHIC)
- The European Alliance of Associations for Rheumatology (EULAR)
- European Medicines Agency's (EMA) Vaccines Working Party (VWP)
- Joint Committee on Vaccination and Immunisation (JCVI) and Van Tam Advisory Group on adverse COVID-19 outcomes
- UK Scientific Advisory Group for Emergencies (SAGE)
- Independent Scientific Advisory Group for Emergencies (Indie_SAGE)
- Centers for Disease Control and Prevention (CDC) Advisory Committee on Immunization Practices (ACIP)
- Food and Drug Administration (FDA) Vaccine Advisory Panel
- The Nuffield Department of Primary Care Health Sciences
- The Nuffield Department of Medicine

Beyond this, inclusion will be dependent upon the credentials of prospective panellists – clinical, academic, or policymaking experience in vaccinology or immunology is essential. Willingness to use Google Forms to submit survey responses is desirable, but not essential. Paper-based versions of each eDelphi round will be provided for those either uncomfortable or unable to use this platform. Prospective panellists will be excluded, however, if they are unable to commit to the full study duration or their expertise is entirely paediatric.
Invitation to participate will be sent via email and managed by the primary investigator. When publically available, the primary investigator will follow up with invitations by telephone. Email invitation will outline the aims of the study, participation details, the level of commitment expected and the inclusion and exclusion criteria specified. To maximise recruitment, those contacted will also have the opportunity to signpost figures in their network that adhere to the inclusion and exclusion specified.
Those that accept to participate will be allocated random identification numbers. Panellists will not be known to one another until the end of data collection. Pre-read materials will also be distributed. In this, panellists will be provided with a panellist information sheet, a brief rationale of the study, executive summaries of relevant steering group research outputs, and a consent form. Executive summaries include a systematic review into differential vulnerability to COVID-19 [23], a phenotyping methodology paper [publication imminent], and real-world evidence for differential vaccine response and COVID infection outcomes (OCTAVE [24] and INFORM [25] studies,

respectively). Consenting panellists will be asked to sign and return their consent form to researchers and retain a copy for their records.
Panellists will be encouraged to ask investigators any clarifying questions on the pre-read materials or study design before the first round begins. The panellist information sheet will also be presented prior to each active eDelphi round to remind panellists of study objectives and their rights to withdraw.
Panellists who fail to respond to an eDelphi round after three consecutive email reminders will be defined as withdrawn. Panellists can also make their own requests to withdraw, however, data collected up to that point of participation cannot be erased. To assess potential attrition bias, the number, percentage and characteristics of withdrawn panellists will be reported and compared to those that continue to participate. A withdrawal rate greater than one–third would be considered an unacceptable loss to follow up. In this instance, the study would be discontinued and recruitment re-opened.

Questionnaire Design:

The stated objectives of this study require that consensus be built around the definition of adult immunosuppression and digital phenotypes based on observed vulnerability to severe COVID-19 outcomes. This involves establishing and risk-stratifying constituent conditions and determining their dependencies (time/ dose etc.).
To assess this, panellists will be presented with the complete list of conditions that, in accordance to UK criteria for immunosuppression (Green Book Chapter 14a [12, Appendix 1]), would confer immunosuppressed status amongst adults. This resource has been selected on account of its expansiveness, its influence over vaccine allocation in the UK during the study period and its continuity with the systematic literature review included in pre-read materials. Leveraging their professional experiences and their understanding of pre-read findings, panellists will be asked to assess the appropriateness of each condition for inclusion in a definition of immunosuppression and to then evaluate their respective risk level in relation to COVID-19. The latter questions will be presented via Likert scale and binary ‘Higher Risk Immunosuppressed’ vs ‘Lower Risk Immunosuppressed’ options. Once this is completed, panellists will repeat this exercise for immunosuppressed conditions that are absent from the UK definition but are cited in comparable international resources (Immunisation Guidelines for Ireland [26], the Canadian Immunization Guide [27], the Australian Immunisation Handbook [28], the New Zealand Immunisation Handbook [29], USA Yellow Book [30], USA Pink Book [31] amongst others). Finally, consensus statements on how drug-management, time since diagnosis/ last treatment, duration of treatment and duration of remission may modify vulnerability to COVID-19 will be presented via Likert agreement scale; these will be followed by more generalised consensus statements on the challenges associated with defining, treating, and protecting immunosuppressed patients from disease.
Collectively, these exercises will enable researchers to identify redundancies and omissions in the UK working criteria for immunosuppression and their respective vulnerabilities to severe COVID-19 outcomes; this data will then inform the construction of a risk-stratified phenotype of the patient spectrum that will be evaluated in the second eDelphi round and refined via the final discussion group. Although panellists will not be able to skip any questions presented, they will be able to indicate uncertainties in their answers. Optional feedback forms, again hosted on Google Forms, will be distributed via email between consensus building rounds to clarify or refine questionnaire items if needed. Panellists will also be provided with a summary of results for each round to inform their subsequent responses and the concluding debate. Areas of agreement and disagreement will be discussed during the final discussion group.

Data Protection:

All study members will endeavour to protect eDelphi panel rights to privacy and informed consent, including adhering to the Data Protection Act, 1998 [33]. Each round will only collect the minimum required information for study purposes; panellists will not be known to each other. The primary investigator, however, will be required to know the panellists' details for administrative purposes. Panellist data, including consent forms, completed surveys and discussion audio files and transcripts, will be retained for 18 months before being destroyed.

eDelphi questionnaire rounds will be conducted on Google Forms [34]. Google Forms' functionalities include customisable questionnaire items, one-time completion, advanced security measures (data encryption, privacy protections, malware protections etc.), real-time data insights and automated Excel spreadsheet generation and download. Paper-based copies of this questionnaire will be distributed to any panellist that declares discomfort using this platform, however. All panellists will be made aware of the importance of not sharing any sensitive or identifying information about patients in free text questionnaire items.

The final discussion groups will be hosted remotely on Microsoft Teams. Three discussion groups will be organised in total, breaking panellists into three groups based on time zone. Four time slots will be offered for each group. The time slot that receives the most votes will be taken forward. Panellists that are unable to attend any time slot offered will be connected to a Google Forms containing all items that will be discussed. This will ensure all panellists have been provided with the opportunity to contribute to final data collection. Panellists that can attend their final discussion group will be asked to turn their cameras off and to not identify themselves by name at any point over the course of discussion. Attendees will be reminded that discussions are recorded.

Only the study steering group will have access to study data. Computer-based information will be held securely and password protected as standard. All data will be stored on the secure web server, ORCHID [35], hosted by the Nuffield Department of Primary Care Health Sciences. Access will be restricted by user identifiers, passwords, and multi-factor authentication. Electronic data will be backed up every 24 hours to both local and remote media in an encrypted format.

Panellists will be offering their expertise within their capacity as a clinical, research or policy professional. Panellists that consent to being named will be listed as co-authors in all study outputs; those that wish to remain anonymous will be acknowledged as part of the DESTINIES Consortium where only professional affiliation will be listed. Study results will be made available to the public as well as relevant policymakers and academic institutions. Oversight from the European Alliance of Associations for Rheumatology (EULAR) People with Arthritis/ Rheumatism across Europe (PARE) Community will ensure that study results are available in a patient-accessible format.

Results

Aggregated results of panellist response rate, level of agreement for each measure and condition risk ranking will be calculated with R version 4.3.1 (Vienna, Austria)[32]. As per Diamond and colleagues [14], consensus is reached when ≥75% of panellists agree on each item disputed. Analysis will be quality assured by the statistical supervision available within the study steering group. Areas of consensus and continued dissent will be content analysed (inductive), quantified and visualised via distributions of panel results.

Discussion

The present protocol describes the research design and intended methodology for an eDelphi study to build consensus around the definition and risk stratification of adult immunosuppression in adult in

the context of COVID-19. This work is a response to urgent calls to improve the precision of immunosuppressed disease surveillance [36] - something that is impossible without first establishing a universally accepted, clinically meaningful and health record compatible means of subdividing this diverse risk group. If fully executed, this protocol will achieve just this.

This study will be unique in its ability for panellists to leverage authors' literature reviews and real-world evidence for differential immunosuppressed COVID-19 outcomes as pre-read materials for panellists. Likewise, the research group conducting this work has a global network of collaborators to call upon as panellists, including national and international health agencies and their respective vaccine advisory groups. Given the global implications of this work, it is our intention to secure a cross-continental panel with the highest possible calibre of panellists.

However, we anticipate that it will be difficult to achieve consensus on all questionnaire items at the level specified. The sheer scale and complexity of immunosuppression as a clinical risk group invites debate and likely ongoing disagreement. We predict that there may be discrepancies between the risks reported by condition-specific and condition-general panellists, for example. It is possible that condition-specific experts will report disproportionate vulnerability amongst their own patients. Likewise, geographical differences between panellists are likely to affect consensus. Those from less economically developed contexts may report elevated risks than those from contexts where medical provision is more assured. That said, there is great advantage to capturing ongoing areas of dissent between international experts. Doing so will only improve the rigour of this investigation and the nuance of study insights and outputs that result.

Acknowledgements

ML is the principle author of this paper, responsible for study conception, design and write-up of the present protocol. ML will act as the principle investigator mentioned within. LL, IM, JO and RH proofed this work, providing suggested edits and commentary. Remaining authors are part of the steering group the protocol cites.

Conflicts of Interest

No separate funding has been received for this study.

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Abbreviations

ACIP: Advisory Committee on Immunization Practices
CDC: Centers for Disease Control and Prevention
CEPI: Coalition for Epidemic Preparedness Innovations
CMR: Computerised Medical Record
CREDES: Conducting and Reporting Delphi Studies
DESTINIES: eDElphi STudy to defINe and risk-stratify ImmunosupprESsion
EMA: European Medicines Agency
EULAR: The European Alliance of Associations for Rheumatology
EULAR PARE: The European Alliance of Associations for Rheumatology People with Arthritis/ Rheumatism across Europe
FDA: Food and Drug Administration
GACVS: Global Advisory Committee on Vaccine Safety
GHIC: The Global Immunocompromised Health Coalition
Indie_SAGE: Independent Scientific Advisory Group for Emergencies
JCVI: Joint Committee on Vaccination and Immunisation

Oxford-RCGP RSC: Oxford-Royal College of General Practitioners Research and Surveillance Center
ORCHID: Oxford RCGP Clinical Informatics Digital Hub
SAG: Scientific Advisory Group
SAGE: Scientific Advisory Group for Emergencies
VWP: Vaccines Working Party
WHO: World Health Organisation

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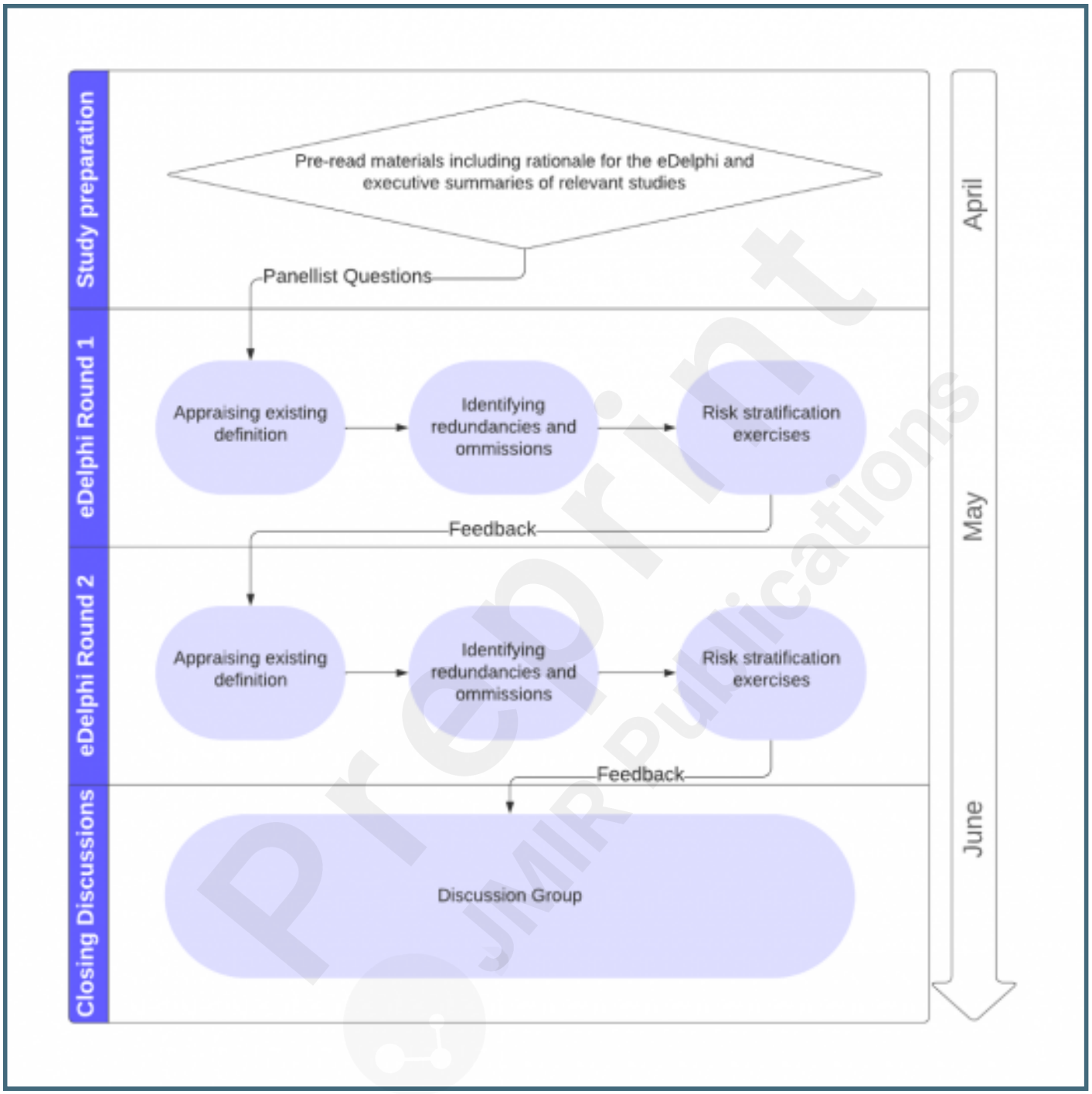
Supplementary Files

Figures

Schematic of the DESTINIES Study Timeline.



Multimedia Appendixes

Definition of immunosuppression in adult populations as per Green Book Chapter 14a Criteria.
URL: http://asset.jmir.pub/assets/01038c249b1e18adb254c16470984984.docx