Immunoglobulin
Sub Regional Assessment Panel

East of England Immunoglobulin Assessment Panel

Based at:

Cambridge University Hospitals NHS
NHS Foundation Trust

Core Practice Standards

December 2023

Immunoglobulin Sub Regional Assessment Panel

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Contributions by:

David de Monteverde-Robb	EOEIAP Pharmacy Lead
Dinakantha Kumararatne	EOEIAP Immunology Lead
Claire McCarthy	EOEIAP Neurology Lead
Ania Manson	EOEIAP Core Panel Member / Immunologist
Rhys Roberts	EOEIAP Core Panel Member / Neurologist
Amanda Cox	EOEIAP Core Panel Member / Neurologist

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1 Contents

Standard details

Standard 1: Panel decisions.

All decisions by the East of England Immunoglobulin Assessment Panel are binding.

All trusts commit to abide by the decisions of the East of England Immunoglobulin Assessment Panel. Appeals are to be referred to a peer SRIAP if raised by a patient or clinician who is not a member of the panel.

Birmingham University Hospitals (West Midlands IAP) is our nominated peer IAP.

Standard 2: Clinical approval prior to treatment

All treatment with immunoglobulins requires approval from the EoE IAP. Applications should be sent to: add-tr.iap-eastofengland@nhs.net, or use the MDSAS referral platform (where implemented)

Treatment application forms are available on the EoE IAP webpage: https://www.cuh.nhs.uk/health-care-professionals/east-england-immunoglobulin-assessment-panel-eoe-iap/

There are separate forms for immunomodulation and immunoreplacement therapy.

Class I indications have Group Prior Approval status from the EoE panel provided the consultant recommending treatment is a specialist in the relevant area of medicine and the patient meets the minimum eligibility criteria. Data from all Class I indications for immunoglobulin must be reported monthly to the EoE IAP as aggregated data:

- Number of patients treated with a breakdown for the indications of each patient
- Total grams immunoglobulin used

Class II to Class V indications require patient-specific panel approval before treatment. The panel maintain a record of all applications for these categories automatically.

- **Class II** indications require a single panel member approval, preferably from a specialist in the area of medicine which relates to the request
- **Class III** indications require a consensus panel decision
- **Class IV** indications require a consensus panel decision and IFR approval
- **Class V** indications are automatically rejected

Class II indications only. If there is a clinical emergency that requires immunoglobulin for a Class II indication to be given out of hours and where the panel cannot be contacted or have not responded, approval may be given in exceptional circumstances from the relevant oncall service at the Cambridge University Hospitals where reference to the clinical guidelines for immunoglobulins has been made and both parties are satisfied that immunoglobulin is indicated (see selection criteria), no exclusion criteria are present and immunoglobulin is the appropriate treatment at the stage of treatment (taking into account possible alternative therapies). The panel must still be informed of the application for treatment.

Standard 3: Reporting outcome measures.

Reports of efficacy and treatment outcome to the regional panel

- Outcomes of all Class III-V indications must be discussed at regional IAP meetings or IAP subpanels (immunology, neurology or the associated group ENRAD).
    - Class V indications are automatically rejected unless in the most exceptional of circumstances
- Class II indications will be discussed where they are referred for discussion – either by the treating clinician, by the panel or by the associate Trust clinical or pharmacist lead.
- Class I indications must be reported per calendar month as aggragated data by each Trust.

Standard 4: All use of immunoglobulins to be notified to the EoE IAP

In line with the CQUIN for immunoglobulins and the basis for the national Sub-Regional IAP network, all use of immunoglobulins must be notified to the affilitate regional panel.

All new immunoglobulin treatments must be;

- Clinically approved by the EoE IAP
- Used in line with emergency procedures (as specified in the regional immunoglobulin treatment guidelines) and retrospectively notified to the EoE IAP. This can be included in end of month data.

Standard 5: Notification of delay or cancellation of treatment.

Any patient whose treatment is cancelled or delayed by a duration of 2 weeks or more directly as a consequence of lack of availability of immunoglobulin must be recorded in the Trust incident reporting system (e.g. QSIS) and notified to the EoE IAP.

Each Trust in the EoEIAP region must maintain a mechanism to report immunoglobulin related incidents or safety learning events to the host panel. This should also include loss of product for instance through expiry, breakages or inappropriate storage. This data should be available to report within 2 weeks of a request from the EoE IAP.

Standard 6: Participation in the regional panel

Each EoE IAP Trust must have a designated clinical immunoglobulins lead (consultant – any speciality) and a designated pharmacy lead for immunoglobulins. The clinical and pharmacy leads are responsible for:

- The implementation of the work plan for immunoglobulins
- The adherence to core practice standards

- Nomination of local workstream leads – e.g. neurology or haematology

Standard 7: Data sharing.

The EoE IAP is to be provided, for all new immunoglobulin treatments and treatments which are due periodic review, with data to permit the EoE IAP and sub-panels to assess eligibility and efficacy of treatment. This will include patient demographic and clinical data. All Trust Medical Directors and Caldicott Guardians should have a signed Data Sharing Agreement in place with the host EoE Trust (Cambridge University Hospitals) to formalise the data sharing arrangement.

Each EoE IAP associate Trust should have arrangements to provide log-in details to the National Immunoglobulin Database to the following EoE IAP post-holders:

- The East of England IAP Pharmacist Lead
- The East of England IAP Panel Coordinator
- The East of England IAP Senior Pharmacist
- The East of England IAP Immunodeficiency Nurse

At the initiation of therapy, patients should be informed of this data sharing arrangement as part of the consent procress.

Standard 8: Patient consent and review.

All patients should be given information and asked to consent to treatment before receiving immunoglobulins. Patients should be informed that:

- **Transmission of infections from blood.** Immunoglobulins are a blood product. There is therefore an inherent low risk of blood borne infection transmission. Transmission of hepatitis A and parvovirus B19 is thought to be possible, though this is generally not found in clinical experience.

- **Infusion reactions for IVIG treatment**;
  - There is clinical evidence of an association between intravenous immunoglobulins and thromboembolic events such as myocardial infarction, cerebral vascular accident (including stroke), pulmonary embolism and deep vein thrombosis, which is assumed to be related to the relative increase in blood viscosity during infusion.
  - There are case reports of acute renal failure in patients following IVIG
  - Other significant but rare events include aseptic meningitis and haemolytic anaemia.

- **In the event of a national supply shortage.** For long term patients - in times of shortage - treatment plans may need to be modified. This may include delaying treatment, switching to an alternative product, or providing an alternative treatment.

- **Demographic, diagnosis and treatment details** will be entered into the national immunoglobulin database as part of the treatment programme and also shared with the regional IAP and its subpanels.

- Be informed that an NHS clinical panel based in the East of England may periodically review the treatment offered and provide advice on the continuation of immunoglobulin treatment based on patient data.

The EoE IAP provides a unified Patient Information Leaflet for immunoreplacement and immunomodulatory therapy with immunoglobulins which may be used to support the local consent process in line with these standards.

Standard 9: Minimum documentation standards.

All EoE IAP Trusts must link local documents to the relevant forms, standards and guidelines published by the EoE IAP on the www.cuh.nhs.uk website. The EoE IAP site is found by following the healthcare professionals link

The full URL webpage is: https://www.cuh.nhs.uk/health-care-professionals/east-england-immunoglobulin-assessment-panel-eoe-iap/

The documents provided in this resource are:

- The East of England Immunoglobulin Clinical Guidelines
- The EoE IAP Core Practice Standards
- The EoE IAP Terms of Reference
- The Immunoglobulin Patient Information Leaflet to be used in conjunction with local consent forms.
- The Immunomodulation Treatment Authorisation Form*
- The Immunodeficiency Treatment Authorisation Form

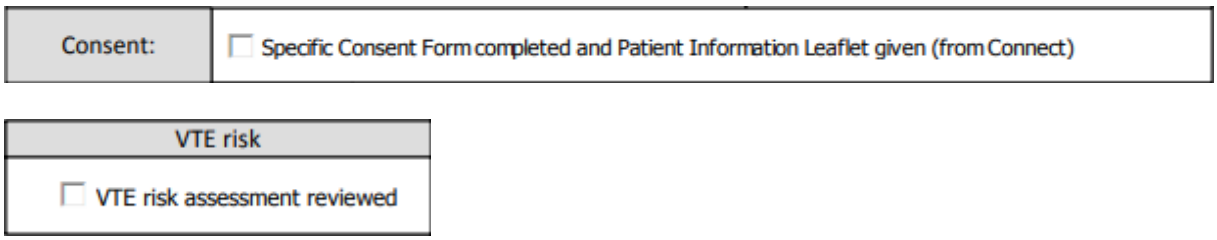
*Or combined with the database treatment form (same link)

Prior to any treatment with immunoglobulins (including those referred to the EOEIAP, emergency treatment and out of hours treatment), the following paperwork or processes must be completed prior to immunoglobulin dispensing / supply / administration:

- A completed **treatment requisition form** (local Trust form)
- A VTE risk assessment
- An consent form relating to immunoglobulin treatment, using the immunoglobulin patient information leaflet as a supporting information tool.

Treatment requisition forms in each treating centre within the EOEIAP should incorporate a statement to confirm consent and a VTE risk assessment review.

See example found in CUH Immunoglobulins requisition form:



Intravenous infusion guides (or monographs) for immunoglobulins should refer to reducing the rate of infusion as appropriate in patients with risk factors for infusions reactions – such as patients with:

- **VTE risks:** Advanced age, hypertension, diabetes mellitus and a history vascular disease or thrombotic episodes, patients with acquired or inherited thrombophilic disorders, patients with prolonged immobilisation, severely hypovolaemic patients, patients with diseases that increase blood viscosity.
- **Acute renal failure risks**: Pre-existing renal insufficiency, diabetes mellitus, hypovolaemia, overweight, concomitant nephrotoxic treatments, age over 65.

Standard 10: Recording of batch numbers.

Administration or supply of immunoglobulins (depending on the hospital system in place) captures the batch number of each vial of immunoglobulin administered or supplied to each patient. This system must be robust, reportable and facilitate reporting to the national immunoglobulin database in a timely manner to allow analysis.

It is not acceptable to record “BN1234576 x 3” as this does not positively confirm each batch number as the same. Paper prescription charts should have appropriate space for peelable batch number stickers from vials to be applied to the prescription chart. It is recommended that prescribing is by vial rather than by dose to facilitate appropriate batch number recording.

Standard 11: Out of hours treatment.

Trusts will adopt a common list of indications for immunoglobulin treatment where group prior approval from the EoE IAP is granted provided a consultant in the condition to be treated is recommending treatment and the patient meets the minimum treatment it is approved to be supplied out of hours.

This list is contained in the regional immunoglobulin treatment guidelines. Those which are approved to be given out of hours are **Class I** indications.

The EOE IAP requires notification of all immunoglobulin treatment. This may be retrospective where delays in treatment may result in patient harm.

Requests for immunoglobulin therapy for other indications require additional approval from the relevant on-call service at CUH. It is expected in most circumstances that decisions regarding treatment for indications other than those listed be delayed until the following morning where usual approval mechanisms apply.

Out of hours:

- The EoE Immunoglobulin Clinical Guidelines specify which indications may proceed out of hours.
- All treatments require a local requisition form to be completed and clinical approval from the panel.
- See standard 2 for further details on obtaining panel approval.
- If there is a risk to life and limb, and where panel approval is pending, pharmacy should supply only enough to last until next working day.

Standard 12: Standardised dosing.

All EoE IAP trusts will apply a standard metric DDW formula to calculate the dose of immunoglobulin for all new patients requiring immunomodulation, unless exception criteria apply (relating to height or weight) – see standard 13.

Males: [(height (cm) – 154) * 0.9] + 50 = Ideal Body Weight
Females: [(height (cm) – 154) * 0.9] + 45.5 = Ideal Body Weight

DDW = IBW + 0.4(ABW – IBW)

Immunomodulation:

- Pregnant patients – use 'booking weight'
- All other patients – apply DDW formula

Immunoreplacement:

- Commence treatment at Actual Body Weight (measured weight) and adjust in line with trough levels and frequency of infection

Example of standard metric DDW formula:

IBW formula		DDW formula	
Males: [(height(cm) - 154) x 0.9] + 50		DDW = IBW + 0.4(ABW - IBW)	
Females: [(height(cm) - 154) x 0.9] + 45.5			
Height (cm)	**ABW (kg)**	**IBW (kg)**	**DDW (kg)**
☐ <154cm (use ABW)			
Use DDW for dosing, unless height < 154cm, weight < 60kg, IBW > ABW			

Standard 13: Standard exceptions to application of the DDW formula.

All EoE acute trusts will apply a common set of rules for the application of the metric DDW formula such that it is used for patients who are to receive immunomodulatory treatment AND the patient is >60kg, >154cm and where the ABW exceeds the IBW.

In the event that the patient is <60kg, <154cm or IBW is more than the ABW, the patient's actual body weight should be used for dosing calculation. If the patient is pregnant, the 'booking weight' should be used.

Points of note for prescribing:

- IVIG prescription chart **must** be used, unless electronic prescription is available

- Height and weight **must** be completed
  Even in low body weight or short stature
  Except neonates → height exempt

- DDW **must** be used except when:
  - Height <154cm (use ABW)
  - Weight <60kg (use ABW)
  - IBW > ABW (use ABW)
  - Pregnancy (use booking weight)
  - Immunoreplacement therapy (use ABW)

Round doses to match vial sizes

- Calculate the dose for total course, then round down to the nearest 5g
- General rule - give largest dose on Day 1

Worked example (1): 179cm, 79kg ♀ 2g/kg over 5 days

IBW = ((179-154) x 0.9) + 45.5
= 22.5 + 45.5
= 68kg

DDW = 68kg + 0.4(79 – 68) = 72.4kg

@ 2g/kg (72.4kg) = 148g (total)
= 145g (round down to the nearest 5g)

= Average of 29g per day

= Give as **30g** on days 1-4, **25g** on day 5 = 145g

Worked example (2): 160cm, 87kg ♂ 0.5g/kg/day for 4 days

IBW = ((160-154) x 0.9) + 50
= 5.4 + 50
= 55.4kg

DDW = 55.4kg + 0.4(87-55.4)

= 68.04kg

@ 2g/kg (68.04kg)	=	136.08g (total)
	=	135g (round down to the nearest 5g)
	=	Day 1 to 4: 35g daily

Standard 14: Response to data requests to panel within 4 weeks

Responses to requests for data from the EOE IAP directly or on behalf of NHS England require a response within 4 weeks unless otherwise specified. This includes patient outcome data, product usage and condition specific reports.

All trusts consent by membership of the EOE IAP group to abide by the terms of the CQUIN for immunoglobulins and the decisions of the EOE IAP. It is a national requirement for stock taking and forecasting responses to be submitted within 4 weeks of request.

Standard 15: Allocations of immunoglobulin products are coordinated and authorised by the EoE IAP

No changes to allocation as agreed with the CMU and pharmaceutical manufacturers or requests for supply in addition to the annual or monthly allocation of immunoglobulins are permitted without written approval by the EoE IAP.

Where there is insufficient stock to support treatment at any of the EoE IAP sites, reallocation of stock within the region is expected prior to requesting additional allocation at a national level.

All communications regarding forecasting or change in allocation of immunoglobulins in line with the national framework must be coordinated through and approved by the EOE IAP before this information is submitted to the Commercial Medicines Unit (CMU) or NHS England.

Transfer of patients between NHS Treatment Centres

Where a patient is transferred between NHS Trusts, sufficient product to support the treatment of the patient until the end of the **current framework year** should be offered to the recipient Trust. If accepted, this is should be:

1. Notified to the EOEIAP – who will amend allocation and confirm the change with the CMU and appropriate pharmaceutical manufacturer
2. Transferred* from the originator Trust
3. Reflected in the master allocation list for the current framework

This rule is in effect in all of the following circumstances

- Transfer from and to an associate EOE IAP Trust

- Transfer from outside the East of England IAP network
- Transfer from within the East of England IAP network to another SRIAP
- Where the product in question is in national shortage.

It is the responsibility of the Trust transferring patients to ensure that remaining patients have sufficient stock to be treated. No Trust receiving a patient from another Trust should be disadvantaged in their ability to access sufficient immunoglobulin product resulting from the decision to take over the care of the patient.

*Where Trusts have sufficient intravenous immunoglobulin capacity, it is accepted that a Trust ought to review the brand prescribed for the patient versus the local formulary choice of immunoglobulin. Trusts should avoid using a single brand of immunoglobulin for 5 or fewer patients. If it is clinically acceptable, the brand should be switched to a suitable formulary choice in the recipient Trust. In this circumstance, a transfer of immunoglobulin product within the framework will not be required.

Standard 16: Clinical Trials involving Immunoglobulins

Communication from Dr Siraj Misbah – 4th Dec 2023
Blood and Infection Programme of Care, NHS England

*Recent trials of some investigational medical products , including bi-specific monoclonal antibodies, have included prophylactic Ig as part of the trial protocol. In assessing such trials, panels are reminded that the use of Ig should be judged against current commissioning criteria for secondary antibody deficiency or any other specific indication, when funding for Ig is **not** provided by the sponsor. For clinical trials involving secondary antibody deficiency, where Ig replacement is being proposed in the absence of an appropriate burden of infection, the sponsor would be required to fund the cost of Ig for the duration of the trial. Continuation of Ig beyond trial completion will be subject to fulfilment of commissioning criteria.*

In response to this the EOEIAP proposes the following system for the management of clinical trials involving the use of immunoglobulin therapy.

The East of England Immunoglobulin Assessment Panel should be notified of intent to commence a novel clinical trial involving immunoglobulin therapy (human normal = HNIg) **prior** to recruitment of patients. Staff working in relation to the trial should provide the trial protocol, copies of consent forms and contact details of the principle investigator.

The EOEIAP should determine for any clinical trial where administration of HNIg is described in the trial protocol:

a) If any patient recruited into a clinical trial involving HNIg could commence treatment in a manner that is not aligned with NHS immunoglobulin commissioning criteria
b) If commercial stock or trial sponsor-funded HNIg stock will be used.
c) That local organisation (prescribing, dispensing, administration and billing) mechanisms are in place to:
    a) Secure and segregate trial sponsor-funded vs. NHS procured stocks

b) To prescribe and administer HNIg with clearly designation of use within the specific clinical trial
c) Ensure dispensing and billing follows the correct process. Trial sponsor stock should not be billed to NHS England. Trial sponsor should not be used other than within the trial protocol.

Where treatment is not aligned with NHS commissioning criteria and treatment may be required following the cessation of the trial

d) The consent process informs the patient that HNIg treatment may have to stop at the end of the clinical trial, pending assessment which may include alternative treatment, e.g. prophylactic antibiotics or alternative immunosuppressant therapy.

The EOEIAP should also be notified when a trial is closed to recruitment.

Where patient treatment is requested to continue following the end of a clinical trial, the patient immediately falls within the NHSE commissioning criteria and must be assessed against criteria for the indication, including stopping therapy where appropriate.

During shortages, NHS procured stocks of immunoglobulin may need to be diverted to greatest clinical need. This may also affect the management of therapy in clinical trials. The EOEIAP will review and assess on individual merits, though clinical trials where immunoglobulin therapy is compared with an established treatment for the condition may be a lower priority than the management of conditions where no effective alternative treatment exists.