Developed for Scotland by the National Plasma Product Expert Advisory Group (NPPEAG)

GUIDELINES ON SELECTION AND USE OF POLYVALENT THERAPEUTIC IMMUNOGLOBULIN PRODUCTS
A range of commercial therapeutic immunoglobulin products is available in Scotland for use in the clinical management of:

a) primary or secondary antibody deficiency disorders (replacement therapy) and

b) a variety of inflammatory and autoimmune diseases (immunomodulatory therapy)

These products are formulated (non-interchangeably) for either intravenous or subcutaneous administration and are invariably derived from large volunteer or remunerated donor plasma pools. All formulations contain IgG as the principal active component at w/v concentrations between 5% and 20%, with variable amounts of IgA along with product-specific stabilising agents and other excipients. Production of therapeutic immunoglobulin products is governed by Good Manufacturing Practice principles and modern production methods of all products are required to incorporate a number of defined, validated viral inactivation or virucidal steps (on the historical basis of hepatitis C transmission by immunoglobulin products in the 1980s/90s). As with all blood products, there are ongoing, unquantifiable risks (actual and theoretical) associated with the use of therapeutic immunoglobulin products in the forms of adverse infusion-related reactions and donor-to-recipient transmission of infectious agents. Disruptions to immunoglobulin supply due to local, national and global issues have happened on an intermittent and unpredictable basis in relatively recent times as a result of factors such as plasma shortages, licensing difficulties or individual product manufacturing failures. This has invariably had a significantly adverse effect on the organisation of care for patients being treated with therapeutic immunoglobulins.

Information and advice on therapeutic usage of polyvalent immunoglobulin products in the NHS in Scotland is available in the relevant national clinical guideline (2nd Edition).

The recommendations below are intended to act as quality standards for immunoglobulin selection and clinical use in the NHS in Scotland. Guiding principles underlying these recommendations are to define and promulgate good practice in:

- Ensuring that patient care and patient safety are paramount in the acquisition, distribution, prescription and administration of therapeutic immunoglobulin products
- Maximising access to, availability of and benefit from therapeutic immunoglobulins for patients with conditions which are responsive to replacement or immunomodulatory therapies
- Minimising clinical risk associated with use of therapeutic immunoglobulin products
- Minimising any wastage in the clinical use of therapeutic immunoglobulin products
- Maximising the financial efficiency of prescription and use of therapeutic immunoglobulin products

**General Considerations**

1) On the basis of current, available evidence NPPEAG regards available immunoglobulin preparations as therapeutically equivalent for all indications.

2) Diversity in availability of a number of immunoglobulin preparations for use within the NHS in Scotland through the national contracting process is advantageous as a safeguard against fluctuations or failures in availability of individual products and for supporting choice in acceptable and tolerable product selection and range for patients on life-long treatment with immunoglobulin.

3) Product availability in the NHS in Scotland should encompass both intravenous and subcutaneous formulations.
4) Immunoglobulin products should be administered according to the individual manufacturers’ instructions, particularly in respect of infusion rates.

**Change of Immunoglobulin Product**

Product change may be elective or the result of forced necessity, undertaken for reasons of a) clinical desirability (adverse reactions, lack of efficacy, health co-morbidities or planned switching between intravenous and subcutaneous treatments), b) access/supply problems relating to a particular product or c) financial management factors. In either event, the following quality and safety considerations would apply.

1) Immunoglobulin products are not regarded as interchangeable when used for either antibody replacement or immunomodulatory therapy.

2) Changing immunoglobulin product, at least in the context of patients with primary immunodeficiency (PID), is associated with a significant increase in adverse events. An elective change from a product which is effective and well tolerated, in the absence of clinical need, is not considered an optimal approach to individual patient management. In the absence of unavoidable, extenuating circumstances PID patients already established on treatment should not undergo product changed for non-clinical reasons (though particular circumstances may necessitate such actions on occasion). There is no information available to guide development of similar recommendations about practice in conditions other than PID.

3) Patient safety must be given paramount consideration when immunoglobulin products are changed. This requires that any changeover is made in a manner which maximises attention to health and safety as well as clinical utility. This should include enhanced patient monitoring during initial infusions with a new product. Changes to new versus old infusion regimes may be necessary during the initial phase of treatment and during ongoing infusions, as recommended by the manufacturer of the new product. A change in product brings operational risks in regard to transmission of blood borne agents and particular attention is required to ensure robust mechanisms for patient monitoring and rapid product traceability. These issues also have relevance to adverse, infusion-related events.

4) Safety, training, monitoring and product traceability issues apply equally to hospital-based and home-based patients receiving immunoglobulin therapy. Formal retraining and short-term observation of home therapy patients will be required at product changeover.
**Batch Management**

**a) Replacement Therapy**

1) Product detail and batch number(s) must be contemporaneously and accurately recorded for every episode where immunoglobulin is infused (including home-based infusions).

2) Minimising short-term and lifelong exposure to plasma donor numbers and facilitating traceability are central factors in reducing and managing clinical risk.

3) Utilising the minimum number of product batches possible (ideally unitary but to a maximum of two) within a single infusion event, as determined by local circumstance, is considered best practice.

4) Mixed use of different immunoglobulin products or formulations within a single infusion event is not justifiable under any circumstances.

5) On occasions where the aim of minimising batch numbers requires the issue from stock of bottles which in total exceed the prescribed dose the excess should normally be administered rather than discarded, unless there are specific contraindications to such practice (such as unstable cardiac failure, severe renal impairment or dose-related adverse effects). This specific element of guidance from NPPEAG is regarded as flexible and for discretionary implementation according to local specialist practice.

6) The dose issued/administered should not be decreased below the prescribed dose solely in order to achieve batch consistency within a single infusion event.

**b) Immunomodulatory Therapy**

1) Product detail and batch number(s) must be contemporaneously and accurately recorded for every episode where immunoglobulin is infused (including home-based infusions).

2) Minimising exposure to plasma donor numbers and facilitating traceability are central factors in reducing and managing clinical risk.

3) Utilising the minimum number of product batches possible within a single infusion event, as determined by local circumstance, is considered best practice.

4) Mixed use of different immunoglobulin products or formulations within a single infusion event is not justifiable under any circumstances.

5) The dose issued/administered maybe issued above/below the prescribed dose in order to achieve batch consistency within a single infusion event. In practice, following a body weight measurement, clinicians should prescribe their recommended dose by rounding up or down (preferably down in the high dose setting) to the nearest whole vial size. The adjustment should not exceed 5 grams (and never be >10% of total dose) in order to avoid administering a clinically significant change of dose.

These good practice statements are regarded by NPPEAG as appropriate, readily auditable exemplars of attainable good practice in the use of therapeutic immunoglobulins. Their adoption by clinical users and incorporation into relevant local governance and quality management systems is recommended. Clinicians should consider their prescribing practices when they order such drugs and liaison with colleagues in pharmacy will facilitate the most effective and efficient use of product across all patient groups.