

Development of *the Criteria for the clinical use of IVIg in Australia*

(First Edition)

National workshop

A process to review the Australian Health Ministers' Advisory Council (AHMAC) (2000) guidelines commenced in 2004, with the National Blood Authority (NBA) convening a workshop of clinicians and others with an interest in IVIg to gather information about changes in the use of IVIg. The workshop suggested a range of strategies to improve the management of IVIg, including:

- national harmonisation of use and access to IVIg;
- thorough examination of existing data to inform decision making;
- the development of new guidelines with multifactorial criteria for accessing IVIg that provide a more practical decision-making framework;
- a representative committee continually reviewing the guidelines;
- the development of an interactive, web-based decision-making approval system for the issue of IVIg and data collection on treatment outcomes;
- audits of the supply of IVIg to encourage accountability; and
- active participation in clinical trials that improve the evidence base.

Systematic reviews

Systematic literature reviews of the efficacy and risks of treatment with IVIg were undertaken in 2004 and 2006 by Biotext Pty Ltd and the Sydney Health Projects Group (SHPG) (Frommer and Madronio 2006). The aims of the reviews were to:

- identify and critically appraise the scientific literature regarding the efficacy and risks of treatment with IVIg;
- analyse scientific publications, including existing guidelines, which identify the key issues in IVIg therapy; and
- include studies comparing IVIg with other treatments, including immunoglobulin administered by other routes, when such other treatments have been studied in comparison with IVIg.

A variety of approaches were used to identify relevant papers, including:

- searching electronic databases of published literature;
- searching the Internet generally for policy documents, government reports and other unpublished or non-mainstream published reports and information;

- cascade searching (e.g. from reference lists of key articles); and
- contacting key researchers.

Electronic databases and other sources were searched for papers published from 1982 to 2005. Information from these papers was extracted into a summary table sorted by condition. Each condition was then assessed and an overall conclusion added. The strength of the evidence was classified according to the categories shown in [Table 1](#).

Table 1 Level of evidence categories

Level of evidence categories		
Category	Studies	Evidence
1	High-quality randomised controlled trials (RCTs)	Clear evidence of benefit
2a	Some RCTs and/or case studies	Evidence of probable benefit - more research needed
2b	Some RCTs and/or case studies	Evidence of no probable benefit - more research needed
2c	High-quality RCTs with conflicting results	Conflicting evidence of benefit
3	High-quality RCTs	Clear evidence of no benefit
4a	Small case studies only	Insufficient data
4b	No included studies	-

More than 90 conditions were assessed for IVIg therapy. Despite the proliferation of research and possible indications for IVIg use, the evidence base for IVIg remains patchy and in some cases conflicted. Major gaps exist in the evidence base supporting IVIg use.

In addition, Australian Healthcare Associates reported the *Review of the cost effectiveness of intravenous immunoglobulin in Australia: cost effectiveness analyses of selected clinical uses of intravenous immunoglobulin* in November 2004.

This review analysed the cost effectiveness of IVIg in the following 10 selected conditions: chronic inflammatory demyelinating polyneuropathy (CIDP), idiopathic thrombocytopenic purpura (ITP), Kawasaki disease, polymyositis/dermatomyositis, allogeneic bone marrow/stem cell transplantation (ABM/BMT), IgG subclass deficiency, lymphoproliferative disorders, multifocal motor neuropathy (MMN), toxic epidermal necrolysis/Stevens–Johnson syndrome and ANCA-positive necrotising vasculitis. These conditions accounted for 58% of IVIg use in 2003–04.

Jurisdictional Blood Committee IVIg Working Party

In April 2005, the JBC established the IVIg Working Party to oversee the development of new guidelines based on the findings of the literature review and outcomes of the 2004 workshop. Clinical specialists from the disciplines of neurology, haematology, and immunology were engaged to provide expert advice to the IVIg Working Party.

The IVIg Working Party was to establish a framework for the development of national guidelines governing the supply and use of IVIg in Australia.

Terms of reference

Specifically, the IVIg Working Party was to:

- review the report of the AHMAC Blood and Blood Products Committee — *Review of the use and supply of intravenous immunoglobulins in Australia* (the AHMAC 2000 IVIg guidelines) with respect to its current and future applicability;
- gather quality contemporary information and data from a wide variety of sources, including specialist groups, government agencies, individuals and other stakeholders with an interest in IVIg (including overseas sources);
- invite comment from specialist groups and colleges with particular reference to product use within their profession and taking into account the findings of the following reports
 - the 2004 and 2005 literature reviews on IVIg;
 - the 2004 cost-effectiveness analysis in to selected clinical uses of IVIg in Australia;
 - the report on the IVIg workshop of 26 May 2004;
- draw on national activity (especially via jurisdictional IVIg user groups, the Australian Red Cross Blood Service and the National Blood Authority) to identify emerging needs and trends in the use of IVIg in Australia;
- establish a process to coordinate and analyse input from stakeholder groups;

- conduct one or more consensus forums or conferences of interested groups and individuals to assist in the development of a national consensus;
- develop guidelines based on the best available evidence taking into account consensus use;
- develop a communications plan that facilitates widespread dissemination and uptake of the guidelines; and
- establish a review mechanism that ensures maintenance of their currency.

Membership

Dr Chris Brook (Chair) — Executive Director, Rural and Regional Health and Aged Care Services, Victorian Department of Human Services

Ms Joan Bedford — Senior Portfolio Officer, Health Department of Western Australia

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Secretariat support

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Development and consultation

Discussion paper

In August 2005, a discussion paper about the development of the new guidelines was circulated for comment. Submissions from the clinical community were subsequently synthesised into a report that proposed options for the development of criteria for use. The IVIg Working Party accepted the recommendations of the report.

Targeted development of proformas

The JBC IVIg Working Party determined that proformas should be developed for selected priority conditions only. These included the following:

- All the conditions that together account for approximately 95% of the total national usage of IVIg by volume (2002–06); plus
- Conditions assigned a ‘Category 1’ priority for IVIg therapy by AHMAC in 2000; plus
- Conditions for which the TGA has registered the use of IVIg; plus
- Conditions for which the Biotext (2004) and Frommer and Madronio (2006) systematic reviews found high-level evidence for the use of IVIg; plus
- Any other conditions recommended by consulting specialist clinicians.

As a result, proformas were developed for 36 priority conditions.

Conditions that had been previously listed for consideration in various reviews, such as the Biotext (2004) review, were not examined in detail for one or more of the following reasons:

- individually, they accounted for a very small proportion of the national usage of IVIg (of the order of 0.1% or less);
- research evidence was available to show that IVIg was ineffective for these conditions, or had an adverse effect;
- no research evidence was available to show whether IVIg was effective for these conditions and clinical specialists recommended against the use of IVIg in their management; and
- the conditions were not identified as high-priority conditions by AHMAC in its 2000 report.

Development of the clinical criteria and exposure draft

The development of clinical criteria for the proforma involved the following steps:

1. Draft proformas were written, using information from a variety of sources.
2. The draft proformas were reviewed by individual clinical specialists in immunology, neurology, haematology and dermatology. The drafts were amended in the light of their advice.
3. Additional draft proformas were prepared for conditions identified as priorities by the clinical specialists.
4. The proformas were reviewed by the IVIg Working Party.
5. The proformas were further reviewed by small expert panels in immunology, haematology, and neurology, and then further amended in the light of their advice.
6. Drafts of the proformas were circulated broadly to professional colleges, societies and other organisations, governments, patient groups and individual specialist clinicians with an interest or expertise in the use or management of IVIg inviting comment. Drafts were also considered at a clinician workshop held in Sydney in November 2006.

The clinical criteria

The clinical criteria given in each proforma were set out to cover four major issues:

1. Indication for IVIg use — this specifies the purpose for which IVIg treatment would be considered once the condition has been confirmed using the proposed diagnostic parameters. The indication generally refers to the prevention or management of a particular manifestation of disease.

2. Qualifying criteria — these are *the Criteria* that should be fulfilled if IVIg is to be used. The qualifying criteria generally refer to matters such as patient selection, particular disease characteristics, disease severity, and any requirement for other treatments to have been demonstrably unsuccessful before IVIg is considered. The qualifying criteria are additional to diagnostic criteria.
3. Exclusion criteria — these define the circumstances in which IVIg should not be used in patients who have the specified indication and fulfil the qualifying condition.
4. Review criteria — these are the major clinical factors that should be taken into account when reviewing the progress of a patient who is receiving IVIg. They comprise parameters that indicate the patient's response to IVIg, and may be used to decide whether to cease or continue IVIg use, or to alter the dose or frequency of administration.

In addition to information about clinical criteria, the proformas include a definition of each condition and a brief description of its clinical presentation and the main diagnostic parameters. The clinical criteria are to be used in addition to: a) the diagnostic criteria that may indicate consideration of a patient for the use of IVIg therapy; and b) the category of available evidence on the effectiveness of IVIg therapy for a diagnosed condition.

Clinical workshop

A workshop of clinicians with an interest in IVIg was held in November 2006. Workshop participants agreed that the document ought to recommend IVIg use only in those conditions where:

- a genuine health benefit can be shown to be derived from the use of IVIg; and
- this benefit is supported by evidence

The workshop also identified the need for the system of approval of IVIg usage under the National Blood Agreement to have flexibility and discretion to deal with unusual requests to use IVIg in justifiable circumstances. It was argued that a system that could allow limited one-off approvals for IVIg would strengthen the overall supply and approval mechanism and obviate the need for every rare condition to be covered in the document in detail.

Sources of information and assessment

The clinical criteria for IVIg use were developed by a JBC IVIg Working Party. In accordance with the Working Party's terms of reference, information and data from a wide variety of sources, including systematic reviews of the literature, specialist groups, government agencies and individuals with an interest in IVIg, were considered.

Evidence of benefit categories

The Biotext and SHPG reviews were used to identify the category of evidence on the effectiveness of IVIg therapy for each condition, as derived from the clinical research examined in these documents. Advice from specialists on conditions not reviewed by Biotext or the SHPG was also taken into consideration.

Overall, the systematic reviews demonstrated that, while a large body of evidence about IVIg exists, the quality of research is limited. Given the rarity of many of the conditions and their severity, high-level analytical (i.e. randomised controlled trial-based) evidence is often not available.

Weighing up and integrating information

A high level of concordance was apparent among the various sources of information, including clinicians' recommendations.

Where discrepancies emerged among the various sources of information about the clinical criteria, the final determination was made by clinicians.

Sources of information other than consultations

The proformas were drafted with reference to the following sources of information:

- Written submissions to the NBA from stakeholders. Stakeholders were invited to provide submissions on (i) a 2005 paper on the [then] current status of IVIg use, prepared by the NBA, (ii) the SHPG review (Frommer and Madronio 2006) and systematic review update; and (iii) initial drafts of *the Criteria* for use document.
- Recently published medical textbooks, from which some of the material was used in defining and describing each condition was derived.
- The Biotext (2004) review of the literature on the efficacy of IVIg therapy, covering the period up to 2004.
- The update of the Biotext review conducted by SHPG (Frommer and Madronio 2006). This mainly focused on new literature, particularly randomised controlled trials, published during 2004–05.
- Clinical guidelines and consensus statements from 2004-06 (used to identify additional clinical qualifying, exclusion and review criteria that are currently recommended for use in Australia or overseas). The relevant clinical guidelines and consensus statements were primarily identified by means of: (i) advice from specialist clinicians, based on their knowledge and professional networks; and (ii) searches conducted using Google and MEDLINE. Search terms comprised 'intravenous immunoglobulins' and 'guideline(s)' or 'consensus' or 'review'.

Contributors

Consultants — Sydney Health Projects Group

The Sydney Health Projects Group (SHPG) was commissioned in July 2006 by the National Blood Authority (NBA) to develop clinical criteria for the use of IVIg in Australia.

Clinical consultations

The selection of conditions for proformas and/or the development of the clinical criteria were undertaken in consultation with, or with advice from, 42 clinicians.

Specialist clinicians provided advice on: (i) the draft proformas, with particular reference to the clinical criteria; (ii) any recent reviews, guidelines or consensus statements (2004–06) that

could contribute to the refinement of clinical criteria; and (iii) additional conditions for which proformas should be prepared.

Finalisation and approval

Written submissions and the outcomes of the clinician workshop were then considered by the IVIg Working Party and a panel of clinical experts. The proforma were then further refined in light of their comments.

A second draft of the document was circulated for comment in March 2007. Submissions from this round were considered by the IVIg Working Party and a committee of clinical experts and further amendments made in light of those considerations.

The amended document was presented to the Jurisdictional Blood Committee in May 2007 and finalised in June 2007. This led to the first edition of *the Criteria* being approved by Health Ministers in December 2007 and coming into effect from 3 March 2008.