APPENDIX 1: LITERATURE SEARCH STRATEGY FOR CLINICAL EFFECTIVENESS STUDIES AND ECONOMIC ANALYSIS

OVERVIEW	
Interface:	Ovid
Databases:	BIOSIS Previews <1989 to 2007 Week 18>; CINAHL - Cumulative Index to Nursing & Allied Health Literature <1982 to December Week 1 2007>; EMBASE <1980 to 2007 Week 14>; Medline In-Process & Other Non-Indexed Citations <April 6, 2007>; Medline <1966 to April Week 1 2007> * Note: Subject headings have been customized for each database.
Date of Search:	April 6, 2007
Alerts:	Monthly search updates began April 6 and ran to June 27, 2007.
Study Types:	Systematic reviews; meta-analyses; technology assessments; randomized controlled trials; controlled clinical trials; economic; practice guidelines.
Limits:	Publication years 1980-present Humans English

SYNTAX GUIDE	
/	At the end of a phrase, searches the phrase as a subject heading
.sh	At the end of a phrase, searches the phrase as a subject heading
MeSH	Medical Subject Heading
fs	Floating subheading
exp	Explode a subject heading
$	Truncation symbol, or wildcard: retrieves plural or variations of a word
*	Indicates that the marked subject heading is a primary topic
?	Truncation symbol for one or no characters only
ADJ	Requires words are adjacent to each other (in any order)
ADJ#	Adjacency within # number of words (in any order)
.ti	Title
.ab	Abstract
.hw	Heading Word; usually includes subject headings and controlled vocabulary
.pt	Publication type
.rn	CAS registry number

MULTI-FILE STRATEGY

Line #	Search	Results
1	Ivig.ti,ab.	7290
2	igiv.ti,ab.	504
3	intravenous Ig.ti,ab.	143
4	Immunoglobulins, Intravenous.sh.	6782
5	*immunoglobulin/iv	1915
6	"Intravenous Immune Globulin".ti,ab.	1296
7	or/1-6	13957
8	Intravenous$.ti,ab.	424889
9	Iv.ti,ab.	461144
10	Infusions, Intravenous.sh.	44342
11	or/8-10	850299
12	subcutaneous immunoglobuli$.ti,ab.	75
13	scig.ti,ab.	54
14	igsc.ti,ab.	51
15	or/12-14	162
16	Subcutaneous$.ti,ab.	181525
17	Subcutaneous Tissue.sh.	3463
18	Injections, Subcutaneous.sh.	25477
19	self-infus$.ti,ab.	224
20	self-administ$.ti,ab.	38510
21	Home.ti,ab.	202073
22	Drug Self Administration.sh.	2248
23	Self Administration.sh.	7559
24	Home Care Services.sh.	22217
25	Home Care.sh.	8259
26	or/16-25	446725
27	IgG.ti,ab.	171602
28	Immunoglobuli$.ti,ab.	184914
29	Immune globulin$.ti,ab.	4930
30	Immunoglobulins.sh.	37375
31	*immunoglobulin G/	32952
32	or/27-31	340641
33	11 and 32	27178
34	33 or 7	31547
35	26 and 32	5489

36	35 or 15	5555
37	36 and 34	892
38	(Immunologic Deficiency Syndromes or immune deficiency).sh.	29990
39	(Immunologic adj1 Deficien$ adj1 Syndrome$).ti,ab.	85
40	(Immunological adj1 Deficien$ adj1 Syndrome$).ti,ab.	13
41	(Antibody adj1 Deficien$ adj1 Syndrome$).ti,ab.	274
42	(antibody adj1 deficienc$).ti,ab.	1069
43	(primary adj1 immunodeficien$ adj1 disease$).ti,ab.	630
44	primary immune deficien$.ti,ab.	285
45	primary immunodeficien$.ti,ab.	2799
46	primary immunedeficien$.ti,ab.	4
47	PIDD.ti,ab.	82
48	PID.ti,ab.	3727
49	PIDs.ti,ab.	262
50	agammaglobulinemia.ti,ab.	1928
51	Xla.ti,ab.	806
52	Bruton$.ti,ab.	1563
53	Agammaglobulinemia.sh.	5296
54	X Linked Agammaglobulinemia.sh.	355
55	Hypogammaglobulinemia.ti,ab.	2769
56	Hypogammaglobulinemia.sh.	808
57	hyper-IgM.ti,ab.	913
58	Hyperimmunoglobulinemia M.sh.	193
59	Hyper-IgM Immunodeficiency Syndrome.sh.	5
60	common variable immunodeficien$.ti,ab.	2310
61	CVID.ti,ab.	1081
62	Common Variable Immunodeficiency.sh.	1413
63	or/38-62	45917
64	63 and 37	144
65	63 and (34 or 36)	2038
66	(major clinical study or multicenter study or randomized controlled trial).ti,ab,hw.	1038736
67	(random$ or sham$ or placebo$ or (singl$ adj (blind$ or dumm$ or mask$)) or (doubl$ adj (blind$ or dumm$ or mask$))).ti,ab,hw.	1609181
68	((tripl$ adj (blind$ or dumm$ or mask$)) or (trebl$ adj (blind$ or dumm$ or mask$))).ti,ab,hw.	585
69	((control$ adj (study or studies or trial$)) or rct$1).ti,ab,hw.	2449572
70	((multicent$ or multi-cent$) adj (study or studies or trial$)).ti,ab,hw.	169261
71	((crossover or cross-over) adj (study or study or trial$)).ti,ab,hw.	58664
72	((case control$ or case comparison$) adj (study or studies or trial$)).ti,ab,hw.	157864

73	(Cohort adj1 (study or studies or trial$ or analysis or analyses)).ti,ab,hw.	171889
74	((control$ or major) adj clinical adj (study or studies or trial$)).ti,ab,hw.	764803
75	or/66-74	3893237
76	Randomized Controlled Trial/	135737
77	exp controlled study/	1830904
78	Double Blind Procedure.sh.	44591
79	Single Blind Procedure.sh.	5570
80	Multicenter study.sh.	33223
81	Crossover procedure.sh.	14532
82	Cohort Analysis.sh.	38169
83	(random$ or sham$ or placebo$ or (singl$ adj (blind$ or dumm$ or mask$)) or (doubl$ adj (blind$ or dumm$ or mask$))).ti,ab.	1395870
84	((tripl$ adj (blind$ or dumm$ or mask$)) or (trebl$ adj (blind$ or dumm$ or mask$))).ti,ab.	556
85	((control$ adj (study or studies or trial$)) or rct$1).ti,ab.	333935
86	((control$ or major) adj clinical adj (study or studies or trial$)).ti,ab.	33245
87	((multicent$ or multi-cent$) adj (study or studies or trial$)).ti,ab.	63127
88	((crossover or cross-over) adj (study or studies or trial$)).ti,ab.	59491
89	((case control$ or case comparison$) adj (study or studies or trial$)).ti,ab.	80586
90	(cohort adj1 (study or studies or trial$ or analysis or analyses)).ti,ab.	90401
91	or/76-90	3292573
92	(Multicenter Study or Randomized Controlled Trial or Controlled Clinical Trial).pt.	643137
93	exp Controlled Clinical Trials/	453342
94	Double-Blind Method.sh.	165186
95	Single-Blind Method.sh.	17497
96	Random allocation.sh.	77821
97	Multicenter studies.sh.	12630
98	Cross-over studies.sh.	34820
99	Cohort studies.sh.	74549
100	(random$ or sham$ or placebo$ or (singl$ adj (blind$ or dumm$ or mask$)) or (doubl$ adj (blind$ or dumm$ or mask$))).ti,ab.	1395870
101	((tripl$ adj (blind$ or dumm$ or mask$)) or (trebl$ adj (blind$ or dumm$ or mask$))).ti,ab.	556
102	((control$ adj (study or studies or trial$)) or rct$1).ti,ab.	333935
103	((control$ or major) adj clinical adj (study or studies or trial$)).ti,ab.	33245
104	((multicent$ or multi-cent$) adj (study or studies or trial$)).ti,ab.	63127
105	((crossover or cross-over) adj (study or studies or trial$)).ti,ab.	59491
106	((case control$ or case comparison$) adj (study or studies or trial$)).ti,ab.	80586
107	(cohort adj1 (study or studies or trial$ or analysis or analyses)).ti,ab.	90401

108	or/92-107	2212207
109	75 or 91 or 108	4098174
110	Meta-Analysis.pt.	15585
111	Meta-Analysis.sh. or exp Technology Assessment, Biomedical/	50673
112	((systematic$ adj (literature review$ or review$ or overview$)) or (methodologic$ adj (literature review$ or review$ or overview$))).ti,ab.	38416
113	((quantitative adj (review$ or overview$ or synthes$)) or (research adj (integration$ or overview$))).ti,ab.	1340
114	((integrative adj2 (review$ or overview$)) or (collaborative adj (review$ or overview$)) or pool$ analy$).ti,ab.	5340
115	(data synthes$ or data extraction$ or data abstraction$).ti,ab.	17013
116	(handsearch$ or hand search$).ti,ab.	5515
117	(mantel haenszel or peto or der simonian or dersimonian or fixed effect$ or latin square$).ti,ab.	17754
118	(meta analy$ or metaanaly$ or met analy$ or metanaly$ or health technology assessment$ or HTA or HTAs or biomedical technology assessment$ or bio-medical technology assessment$).ti,ab.	54819
119	(meta regression$ or metaregression$ or mega regression$).ti,ab.	1278
120	or/110-119	153298
121	(Meta Analysis or Systematic Review or Biomedical Technology Assessment).mp.	112869
122	(meta analy$ or metaanaly$ or met analy$ or metanaly$ or health technology assessment$ or HTA or HTAs or biomedical technology assessment$ or bio-medical technology assessment$).ti,ab.	54819
123	(meta regression$ or metaregression$ or mega regression$).ti,ab.	1278
124	((systematic$ adj (literature review$ or review$ or overview$)) or (methodologic$ adj (literature review$ or review$ or overview$))).ti,ab.	38416
125	((quantitative adj (review$ or overview$ or synthes$)) or (research adj (integration$ or overview$))).ti,ab.	1340
126	((integrative adj2 (review$ or overview$)) or (collaborative adj (review$ or overview$)) or (pool$ adj analy$)).ti,ab.	5340
127	(data synthes$ or data extraction$ or data abstraction$).ti,ab.	17013
128	(handsearch$ or hand search$).ti,ab.	5515
129	(mantel haenszel or peto or der simonian or dersimonian or fixed effect$ or latin square$).ti,ab.	17754
130	or/121-129	156848
131	(Meta Analysis or Systematic Review).sh.	49088
132	(meta analy$ or metaanaly$ or met analy$ or metanaly$ or health technology assessment$ or HTA or HTAs or biomedical technology assessment$ or bio-medical technology assessment$).ti,ab.	54819
133	(meta regression$ or metaregression$ or mega regression$).ti,ab.	1278
134	((systematic$ adj (literature review$ or review$ or overview$)) or (methodologic$ adj (literature review$ or review$ or overview$))).ti,ab.	38416
135	((quantitative adj (review$ or overview$ or synthes$)) or (research adj (integration$ or	1340

	overview$))).ti,ab.	
136	((integrative adj2 (review$ or overview$)) or (collaborative adj (review$ or overview$)) or (pool$ adj analy$)).ti,ab.	5340
137	(data synthes$ or data extraction$ or data abstraction$).ti,ab.	17013
138	(handsearch$ or hand search$).ti,ab.	5515
139	(mantel haenszel or peto or der simonian or dersimonian or fixed effect$ or latin square$).ti,ab.	17754
140	or/131-139	144827
141	120 or 130 or 140	163409
142	*Economics/	10180
143	*Economics, Medical/	5910
144	*Economics, Pharmaceutical/	1682
145	exp "Costs and Cost Analysis"/	235015
146	exp Health Care Costs/	108587
147	exp decision support techniques/	48115
148	economic value of life.sh.	48
149	exp models, economic/	20339
150	markov chains.sh.	4097
151	monte carlo method.sh.	14766
152	uncertainty.sh.	3157
153	quality of life.sh.	144968
154	quality-adjusted life years.sh.	3020
155	exp health economics/	154257
156	exp economic evaluation/	70046
157	exp pharmacoeconomics/	40904
158	exp economic aspect/	235379
159	quality adjusted life year/	5946
160	quality of life/	144968
161	exp "costs and cost analyses"/	132534
162	cost containment.sh.	0
163	(economic impact or economic value or pharmacoeconomics or health care cost or economic factors or cost analysis or economic analysis or cost or cost-effectiveness or cost effectiveness or costs or health care cost or cost savings or cost-benefit analysis or hospital costs or medical costs or quality-of-life).sh.	265570
164	health resource allocation.sh.	2902
165	(econom$ or cost or costly or costing or costed or price or prices or pricing or priced or discount or discounts or discounted or discounting or expenditure or expenditures or budget$ or afford$ or pharmacoeconomic or pharmaco-economic$).ti,ab.	652002
166	(cost$ adj1 (util$ or effective$ or efficac$ or benefit$ or consequence$ or analy$ or minimi$ or saving$ or breakdown or lowering or estimate$ or variable$ or allocation or control or illness or sharing or life or lives or affordabl$ or instrument$ or technolog$ or	141777

	day$ or fee or fees or charge or charges)).ti,ab.	
167	(decision adj1 (tree$ or analy$ or model$)).ti,ab.	13003
168	((value or values or valuation) adj2 (money or monetary or life or lives or costs or cost)).ti,ab.	6410
169	(qol or qoly or qolys or hrqol or qaly or qalys or qale or qales).ti,ab.	28587
170	(sensitivity analys$s or "willingness to pay" or quality-adjusted life year$ or quality adjusted life year$ or quality-adjusted life expectanc$ or quality adjusted life expectanc$).ti,ab.	7254
171	(unit cost or unit-cost or unit-costs or unit costs or drug cost or drug costs or hospital costs or health-care costs or health care cost or medical cost or medical costs).ti,ab.	25771
172	(decision adj1 (tree$ or analy$ or model$)).ti,ab.	13003
173	or/142-172	1119660
174	109 or 141	4173006
175	174 and 64	39
176	173 and (64 or 65)	164
177	176 or 175	188
178	*practice guideline/ or *clinical pathway/ or *clinical protocol/ or *consensus development/ or *good clinical practice/	18508
179	Practice Guidelines.sh.	49428
180	exp Consensus Development Conferences/	2914
181	(consensus development conference or consensus development conference nih).pt.	5469
182	guideline.pt.	14104
183	((practice or clinical) adj (guideline? or pathway? or path? or protocol?)).ti,ab.	28719
184	(critical adj (path? or pathway? or protocol?)).ti,ab.	2403
185	(practice parameter$ or position statement$).ti,ab.	4743
186	guideline?.ti.	64236
187	(care adj (map? or path? or plan? or pathway? or consensus)).mp.	13491
188	or/178-187	154528
189	188 or 141	313193
190	189 and 36	53
191	190 or 177	240
192	limit 191 to english language [Limit not valid in: CDSR,ACP Journal Club,DARE,CCTR; records were retained]	215
193	limit 192 to human [Limit not valid in: CDSR,ACP Journal Club,DARE,CCTR,CINAHL,Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations; records were retained]	210
194	limit 193 to yr="1980 - 2007" [Limit not valid in: DARE; records were retained]	210
195	remove duplicates from 194	149
196	176	164
197	limit 196 to english language [Limit not valid in: CDSR,ACP Journal Club,DARE,CCTR; records were retained]	143

198	limit 197 to human [Limit not valid in: CDSR,ACP Journal Club,DARE,CCTR,CINAHL,Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations; records were retained]	142
199	limit 176 to yr="1980 - 1990" [Limit not valid in: DARE; records were retained]	12
200	remove duplicates from 199	12
201	34 not 63	29586
202	201 and (141 or 188)	576
203	remove duplicates from 202	436
204	limit 203 to english language [Limit not valid in: CDSR,ACP Journal Club,DARE,CCTR; records were retained]	399
205	limit 204 to human [Limit not valid in: CDSR,ACP Journal Club,DARE,CCTR,CINAHL,Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations; records were retained]	393
206	limit 205 to yr="2002 - 2007" [Limit not valid in: DARE; records were retained]	250
207	34 and (141 or 188)	617
208	remove duplicates from 207	468
209	limit 208 to english language [Limit not valid in: CDSR,ACP Journal Club,DARE,CCTR; records were retained]	428
210	limit 209 to yr="2002 - 2007" [Limit not valid in: DARE; records were retained]	267
211	limit 209 to yr="1997 - 2007" [Limit not valid in: DARE; records were retained]	370

OTHER DATABASES	
PubMed	Same MeSH, keywords, limits, and study types used as per MEDLINE® search, with appropriate syntax used.
Cochrane Library Issues 1, 2007	Same MeSH, keywords, and date limits used as per MEDLINE® search, excluding study types and Human restrictions. Syntax adjusted for Cochrane Library databases.

Grey literature and hand searches

Dates for Search:	April 2007
Keywords:	Ivig, intravenous Ig, intravenous Immunoglobulin, scig, subcutaneous immunoglobulin, primary immune deficiency, primary immunodeficiency, primary immunedeficiency, agammaglobulinemia, Hypogammaglobulinemia, hyper-IgM, common variable immunodeficiency
Limits:	Publication years 1980-present

*** NOTE:** This section lists the main agencies, organizations, and websites searched**; it is not a complete list.** For a complete list of sources searched, contact CADTH (http://www.cadth.ca).

Health Technology Assessment Agencies

Alberta Heritage Foundation for Medical Research (AHFMR)
http://www.ahfmr.ab.ca

Agence d'Evaluation des Technologies et des Modes d'Intervention en Santé (AETMIS). Québec
http://www.aetmis.gouv.qc.ca

Canadian Agency for Drugs and Technologies in Health (CADTH)
http://www.cadth.ca

Centre for Evaluation of Medicines (Father Sean O'Sullivan Research Centre,
St. Joseph's Healthcare, Hamilton, and McMaster University, Faculty of Health Sciences, Hamilton, Ontario).
http://www.thecem.net/

Centre for Health Services and Policy Research, University of British Columbia.
http://www.chspr.ubc.ca/cgi-bin/pub

Health Quality Council of Alberta (HQCA)
http://www.hqca.ca

Health Quality Council. Saskatchewan.
http://www.hqc.sk.ca/

Institute for Clinical Evaluative Sciences (ICES). Ontario.
http://www.ices.on.ca/

Institute of Health Economics (IHE). Alberta.
http://www.ihe.ab.ca/

Manitoba Centre for Health Policy (MCHP)
http://www.umanitoba.ca/centres/mchp/

Ontario Ministry of Health and Long Term Care. Health Technology Reviews
http://www.health.gov.on.ca/english/providers/program/mas/tech/tech_mn.html

The Technology Assessment Unit of the McGill University Health Centre
http://www.mcgill.ca/tau/

Therapeutics Initiative. Evidence-Based Drug Therapy. University of British Columbia.
http://www.ti.ubc.ca

Health Technology Assessment International (HTAi)
http://www.htai.org

International Network for Agencies for Health Technology Assessment (INAHTA)
http://www.inahta.org

WHO Health Evidence Network
http://www.euro.who.int/HEN

Australian Safety and Efficacy Register of New Interventional Procedures – Surgical (ASERNIP-S)
http://www.surgeons.org/Content/NavigationMenu/Research/ASERNIPS/default.htm

Centre for Clinical Effectiveness (Monash University)
http://www.med.monash.edu.au/healthservices/cce/

Medicare Services Advisory Committee (Department of Health and Aging)
http://www.msac.gov.au/

NPS RADAR (National Prescribing Service Ltd)
http://www.npsradar.org.au/site.php?page=1&content=/npsradar%2Fcontent%2Farchive_alpha.html

ITA - Institute of Technology Assessment
http://www.oeaw.ac.at/ita/index.htm

Federal Kenniscentrum voor de Gezendheidszorg
http://www.kenniscentrum.fgov.be

Danish Centre for Evaluation and Health Technology Assessment (DCEHTA). National Board of Health
http://www.dihta.dk/

DSI Danish Institute for Health Services Research and Development
http://www.dsi.dk/engelsk.html

Finnish Office for Health Care Technology and Assessment (FinOHTA). National Research and Development Centre for Welfare and Health. http://finohta.stakes.fi/EN/index.htm

L'Agence Nationale d'Accréditation et d'Evaluation en Santé (ANAES). Ministere de la Santé, de la Famille, et des Personnes handicappés)
http://www.anaes.fr/anaes/anaesparametrage.nsf/HomePage?ReadForm

Committee for Evaluation and Diffusion of Innovative Technologies (CEDIT)
http://cedit.aphp.fr/english/index_present.html

German Institute for Medical Documentation and Information (DIMDI). Federal Ministry of Health.
http://www.dimdi.de/static/de/hta/db/index.htm

Health Service Executive
http://www.hebe.ie/ProgrammesProjects/HealthTechnologyAssessment

College voor Zorgverzekeringen/Health Care Insurance Board (CVZ)
http://www.cvz.nl

Health Council of the Netherlands
http://www.gr.nl

New Zealand Health Technology Assessment Clearing House for Health Outcomes and Health Technology Assessment (NZHTA)
http://nzhta.chmeds.ac.nz/

Norwegian Centre for Health Technology Assessment (SMM)
http://www.kunnskapssenteret.no/index.php?show=38&expand=14,38

Agencia de Evaluación de Tecnologias Sanitarias (AETS), Instituto de Salud "Carlos III"/Health Technology Assessment Agency
http://www.isciii.es/htdocs/investigacion/Agencia_quees.jsp

Basque Office for Health Technology Assessment (OSTEBA). Departemento de Sanidad
http://www.osasun.ejgv.euskadi.net/r52-2536/es/

Catalan Agency for Health Technology Assessment and Research (CAHTA)
http://www.aatrm.net/html/en/Du8/doc7850.html

CMT - Centre for Medical Technology Assessment
http://www.cmt.liu.se/pub/jsp/polopoly.jsp?d=6199&l=en

Swedish Council on Technology Assessment in Health Care (SBU)
http://www.sbu.se/www/index.asp

Swiss Network for Health Technology Assessment
http://www.snhta.ch/about/index.php

European Information Network on New and Changing Health Technologies (EUROSCAN). University of Birmingham. National Horizon Scanning Centre
http://www.euroscan.bham.ac.uk

National Horizon Scanning Centre (NHSC)
http://www.pcpoh.bham.ac.uk/publichealth/horizon

NHS Health Technology Assessment /National Coordinating Centre for Health Technology Assessment (NCCHTA). Department of Health R&D Division.
http://www.hta.nhsweb.nhs.uk

NHS National Institute for Clinical Excellence (NICE)
http://www.nice.org.uk

NHS Quality Improvement Scotland
http://www.nhshealthquality.org

University of York NHS Centre for Reviews and Dissemination (NHS CRD)
http://www.york.ac.uk/inst/crd

The Wessex Institute for Health Research and Development. Succinct and Timely Evaluated Evidence Review (STEER)
http://www.wihrd.soton.ac.uk/

West Midlands Health Technology Assessment Collaboration (WMHTAC)
http://www.publichealth.bham.ac.uk/wmhtac/

Agency for Healthcare Research and Quality (AHRQ)
http://www.ahrq.gov/

Dept. of Veterans Affairs Research & Development, general publications
http://www1.va.gov/resdev/prt/pubs_individual.cfm?webpage=pubs_ta_reports.htm

VA Technology Assessment Program (VATAP)
http://www.va.gov/vatap/

ECRI
http://www.ecri.org/

Institute for Clinical Systems Improvement
http://www.icsi.org/index.asp

Technology Evaluation Center (Tec). BlueCross BlueShield Association.
http://www.bluecares.com/tec/index.html

University HealthSystem Consortium (UHC)
http://www.uhc.edu/

Health Economic

Bases Codecs. CODECS (COnnaissances et Décision en EConomie de la Santé) Collège des Economistes de la Santé/INSERM
http://www.inserm.fr/codecs/codecsanglais.nsf/(Web+English+Startup+Page)?OpenForm

Centre for Health Economics and Policy Analysis (CHEPA). Dept. of Clinical Epidemiology and Biostatistics. Faculty of Health Sciences. McMaster University, Canada.
http://www.chepa.org

Health Economics Research Group (HERG). Brunel University, U.K.
http://www.brunel.ac.uk/about/acad/herg

Health Economics Research Unit (HERU). University of Aberdeen.
http://www.abdn.ac.uk/heru/

XOHE-IFMPA Database Ltd.
http://www.ohe-heed.com/

The Hospital for Sick Children (Toronto). PEDE Database.
http://pede.bioinfo.sickkids.on.ca/pede/index.jsp

University of Connecticut. Department of Economics. RePEc database.
http://ideas.repec.org

Organizations and Societies

Canadian Immunodeficiency Society
http://www.cisociety.com/index.html
Canadian Immunodeficiency Patient Organization
http://www.cipo.ca/english/literature.htm
Primary Immundeficiency Association
http://www.pia.org.uk/
Immune Deficiency Foundation
http://primaryimmune.org
International Patient Organisation for Primary Immunodeficiency
http://ipopi.org/sitemap.html
European Society for Immunodeficiencies
http://www.esid.org/links.php
Immune Deficiences Foundation New Zealand
http://www.idfnz.org.nz/

Search Engines

Google
http://www.google.ca/

Yahoo!
http://www.yahoo.ca/

APPENDIX 2: CLINICAL DATA EXTRACTION FORM

Data Extraction Worksheet

Reviewer:

Study title:		
Author:		
ID #: Year:		
Methods		
Study design		
Study duration		
Population - Number of patients randomized - Number of patients completing the study		
Diagnosis		
Eligibility criteria		
Country of origin		
Industry sponsorship	☐ Yes ☐ No ☐ Unknown	
Baseline Characteristics Of Study Participants		
- Age - PID diagnosis - Previous Ig treatment - Others		
Interventions		
Outcomes	**With IVIg**	**With SCIg**
EFFICACY Number of patients with infection Severity of infection Length of infection Days lost from work or school due to infections Serum Ig levels Quality of life **SAFETY** - Adverse events - Number of patients withdrawn due to adverse events		
Comments		

APPENDIX 3: ECONOMIC DATA EXTRACTION FORM

Author, year, country	
Study design	
Study population	
Intervention and comparator	
Clinical outcome measure*	
Cost outcome measure**	
Incremental outcome***	
Main results and conclusion	
Comments	

* Includes QALY, LYS, and health utility
** Includes weekly/monthly/yearly costs associated with reduction of infection, managing adverse events, medicine, healthcare resources use, and lost time.
*** Incremental cost-utility, ICER, and incremental cost per life year saved

APPENDIX 4: CLINICAL TRIAL QUALITY ASSESSMENT FORM

Reference Reviewer	
	Score
Study design 1. Large RCT (Over 50 in each arm): 5 points 2. Small RCT: 3 points 3. Prospective: 2 points 4. Retrospective: 1 point If RCT*: - Randomization appropriately described? - Blinded? - Blinding appropriately described? - Withdrawals described? *Score (An RCT gets full points if all 4 characteristics are addressed. Half a point is deducted for each characteristic not addressed)	
Study performance 1. Patient selection 2. Description/specification of the intervention 3. Specification and analysis of study 4. Patient disposal 5. Outcomes reported Score (Info missing 0 point, Info limited 1 point, Info satisfactory 2 points)	
Overall Score	
Category A (overall score 11.5-15.0): High quality – high degree of confidence in study findings B (overall score 9.5-11.0): Good quality – some uncertainty regarding the study findings C (overall score 7.5-9.0): Fair to good quality – some limitations that should be considered in any implementation of study findings D (overall score 5.5-7.0): Poor to fair quality – substantial limitations in the study; findings should be used cautiously E (overall score 1-5.0): Poor quality – unacceptable uncertainty for study findings	

APPENDIX 5: EXCLUDED REPORTS (CLINICAL)

Inappropriate study design (e.g., reviews, case studies)

Berger M. Subcutaneous immunoglobulin replacement in primary immunodeficiencies. *Clin Immunol* 2004;112(1):1-7.

Haddad L, Perrinet M, Parent D, Leroy-Cotteau A, Toguyeni E, Condette-Wojtasik G, et al. Étude comparative du coût du traitement à domicile des immunoglobulines intraveineuses ou sous-cutanées a visée substitutive. *Rev Med Interne* 2006;27(12):924-6.

Reid B, Van Allen D, LaGrange CA, Boissonneault N. Protocol recommendations for administration of intravenous immunoglobulin in Canada. *J Infus Nurs* 2006;29(3):158-64.

Rinaldi M, Bardelli F, Rampazzo R, Lusuriello P, Messori A. Effectiveness of immunoglobulins for the prevention of systemic infections: a metaanalysis of 8 clinical studies in premature infants. *Clin Drug Invest* 1995;10(6):328-36.

Hernandez M, Bastian JF. Immunodeficiency in childhood. *Current Allergy & Asthma Reports* 2006;6(6):468-74.

Niehues T, Reichenbach J, Neubert J, Gudowius S, Puel A, Horneff G, et al. Nuclear factor κB essential modulator-deficient child with immunodeficiency yet without anhidrotic ectodermal dysplasia. *Journal of Allergy & Clinical Immunology* 2004;114(6):1456-62.

Quinti I, Pierdominici M, Marziali M, Giovannetti A, Donnanno S, Chapel H, et al. European surveillance of immunoglobulin safety--results of initial survey of 1243 patients with primary immunodeficiencies in 16 countries. *Clin Immunol* 2002;104(3):231-6.

Finsterer J. Treatment of immune-mediated, dysimmune neuropathies. *Acta Neurol Scand* 2005;112(2):115-25.

Chinen J, Shearer WT. Subcutaneous immunoglobulins: alternative for the hypogammaglobulinemic patient? *Journal of Allergy & Clinical Immunology* 2004;114(4):934-5.

FDA licenses solvent/detergent-treated immune globulin IV. *P & T* 1994;19(8):746+749.

van der Meché FG, van Doorn PA. The current place of high-dose immunoglobulins in the treatment of neuromuscular disorders. *Muscle Nerve* 1997;20(2):136-47.

Cross AS. Intravenous immunoglobins (IVIGs) to prevent and treat infectious diseases. *Advances in Experimental Medicine & Biology* 1995;383:123-30.

Steele RW, Burks AW, Williams LW. Intravenous immunoglobulin: new clinical applications. *Annals of Allergy* 1988;60(2):89-94.

Bennett WG, Watson RA, Heard JK, Vesely DL. Home hyperalimentation for common variable hypogammaglobulinemia with malabsorption secondary to intestinal nodular lymphoid hyperplasia. *Am J Gastroenterol* 1987;82(10):1091-5.

Söderström T, Söderström R, Enskog A. Immunoglobulin subclasses and prophylactic use of immunoglobulin in immunoglobulin G subclass deficiency. *Cancer* 1991;68 Suppl(6):1426-9.

Inappropriate population

Rubin RH. Cytomegalovirus in solid organ transplantation. *Transpl Infect Dis* 2001;3:Suppl-5.

Boughton BJ, Jackson N, Lim S, Smith N. Randomized trial of intravenous immunoglobulin prophylaxis for patients with chronic lymphocytic leukaemia and secondary hypogammaglobulinaemia. *Clin Lab Haematol* 1995;17(1):75-80.

Jurlander J, Geisler CH, Hansen MM. Treatment of hypogammaglobulinaemia in chronic lymphocytic leukaemia by low-dose intravenous gammaglobulin. *European Journal of Haematology* 1994;53(2):114-8.

Inappropriate outcomes, wrong or no comparator

Chouksey A, Duff K, Wasserbauer N, Berger M. Subcutaneous immunoglobulin-G replacement therapy with preparations currently available in the United States for intravenous or intramuscular use: reasons and regimens. *Allergy Asthma & Clinical Immunology* 2005;1(3):120-30.

Eijkhout HW, van den Broek PJ, Van der Meer JWM. Substitution therapy in immunodeficient patients with anti-IgA antibodies or severe adverse reactions to previous immunoglobulin therapy. *Neth J Med* 2003;61(6):213-7. Available: http://www.zuidencomm.nl/njm/getpdf.php?t=a&id=75 (accessed 2007 Mar 19).

Brennan VM, Cochrane S, Fletcher C, Hendy D, Powell P. Surveillance of adverse reactions in patients self-infusing intravenous immunoglobulin at home. *J Clin Immunol* 1995;15(2):116-9.

Williams P, White A, Wilson JA, Yap PL. Penetration of administered IgG into the maxillary sinus and long-term clinical effects of intravenous immunoglobulin replacement therapy on sinusitis in primary hypogammaglobulinaemia. *Acta Otolaryngol* 1991;111(3):550-5.

Sorensen RU, Kallick MD, Berger M. Home treatment of antibody-deficiency syndromes with intravenous immune globulin. *Journal of Allergy & Clinical Immunology* 1987;80(6):810-5.

Ashida ER, Saxon A. Home intravenous immunoglobulin therapy by self-administration. *J Clin Immunol* 1986;6(4):306-9.

Waniewski J, Gardulf A, Hammarström L. Bioavailability of gamma-globulin after subcutaneous infusions in patients with common variable immunodeficiency. *J Clin Immunol* 1994;14(2):90-7.

Adler R, Safadi R, Caraco Y, Rowe M, Etzioni A, Ashur Y, et al. Comparison of immune reactivity and pharmacokinetics of two hepatitis B immune globulins in patients after liver transplantation. *Hepatology* 1999;29(4):1299-305.

Duplicate

Gardulf A, Bjorvell H, Andersen V, Bjorkander J, Ericson D, Froland SS, et al. Lifelong treatment with gammaglobulin for primary antibody deficiencies: the patients' experiences of subcutaneous self-infusions and home therapy. *J Adv Nurs* 1995;21(5):917-27.

APPENDIX 6: CLINICAL RESULTS (IVIG VERSUS SCIG)

Trial	No. of patients with infections	Severity of infections	Length of infection	Serum Ig level	Days lost from work/ school	Adverse Events (AEs)	No. of patients withdrawn due to AEs
Clinical Studies							
Chapel, 1999[25]	No differences between IV and SC	**IV**: 2 major infections **SC**: 1 major infection	No statistically significant differences	**IV**: trough IgG 7.8 to 8.7 g/L (quartiles 5.8 to 9.8) **SC**: trough IgG 8.0 to 9.1 g/L (quartiles 6.8 to 12.0)	12 days in both IV and SC	**IV**: 34/684 (5.0%) infusion reaction rate 51/684 (7.5%) systemic AE rate **SC**: 127/1222 (10.4%) infusion rate 56/1222 (4.6%) systemic AE rate	**IV**: 0/9 **SC**: 3/13
Gardulf, 2006 [22]	**IV:** NR **SC**: 5 pt: no infection at all 47 pt: with infections: - Children: 13/15 - Adults: 34/37 35 pt: 1 to 3 infections 12 pt: 4 infections and more.	**IV**: NR **SC**: 114 RTI (13 LRTI, 101 URTI) (90% mild, 1 serious); 5 GI infections (2 serious)	NR	**IV**: Children**:** trough 7.8 g/L SD 1.9) Adults: 8.6 g/L (SD: 2.2) **SC**: Children: trough 9.2 g/L (SD: 2.4) ($p < 0.001$) Adults: 8.9 g/L (SD: 2.1) ($p < 0.001$)	**IV:** NR **SC**: 16/52 pt missed days from school or work; 6/15 children missed 1 to 9 days; 10/37 adults missed 1 to 36 days	**IV**: NR **SC**: 28/2297 (1%) infusions caused adverse reactions (24 mild, 3 moderate, 1 severe) (17 raise in body temp; 11 dizziness, malaise, chills, non-generalized skin reactions) 12 adults, 1 child with adverse reactions	**IV:** NR **SC**: 2/60 (1 adult with severe systematic adverse reaction, 1 moderate local tissue reaction)

Trial	No. of patients with infections	Severity of infections	Length of infection	Serum Ig level	Days lost from work/ school	Adverse Events (AEs)	No. of patients withdrawn due to AEs
						641/2297 (28%) infusions caused local, transient tissue reactions (98% mild)	
Gardulf, 1995 [31]	NR	NR	NR	**IV**: 4.9 g/L **SC**: 7.3 g/L	NR	**IV**: 192 adverse reactions /1416 infusions (14%) (146 mild, 46 moderate) **SC**: 106 systemic adverse reactions /33168 infusions (0.03%) (100 mild, 6 moderate)	**IV:** NR **SC**: 2
Gardulf, 1991[27]	**IV**: NR **SC**: 2 hospitalizations (1 pneumonia; 1 pneumonia + otitis media); 1 death (septicemia)	NR	**IV + IM**: preceding 5 yrs, 0.7 days/yr in hospital due to respiratory infection **SC**: 0.2 days/yr in hospital due to resp infection	**IV:** 3.3 g/L (range: 0.4 - 12.5) **SC**: 8.1 g/L (4.6 - 16.7)	NR	**IV** 179 adverse reactions/387 infusions (46.3%) (179 mild; 0 severe) **SC**: 30/3232 (0.93%) (30 mild; 0 severe)	NR
Ochs, 2006[29]	**IV:** NR **SC**: 49/51 (96%)	**IV:** NR **SC**: 4 hospitalized (2 severe infections)	**IV:** NR **SC**: 12 days in hospital total (0.23 days/pt.year); 12 days of febrile episodes	**IV**: 786 mg/dL **SC**: 1040 mg/dL	**IV:** NR **SC**: 32/51 (62.7%) missed a total of 192 days of	**IV:** NR **SC**: 2584/3656 infusions with adverse events; 9/51 (14%) pts reported a	NR

Trial	No. of patients with infections	Severity of infections	Length of infection	Serum Ig level	Days lost from work/ school	Adverse Events (AEs)	No. of patients withdrawn due to AEs
					school or work	total of 10 adverse events	
Pac 2005 [30]	**IV**: 34 RTI episodes, **SC**: 17 RTI episodes	**IV**: 1 pneumonia, 9 bronchitis **SC**: 2 bronchitis	**IV**: 262 days on antibiotics **SC**: 138 days on antibiotics	**IV**: 5.33 g/L (3.48 to 7.44) **SC**: 6.70 g/L (3.58 to 8.97)	NR	**IV**: 1 patient **SC**: 1 patient	NR
Quality of Life Studies							
Kittner 2006 [32]	Likert scale: evaluating patient's attitude toward SCIg home therapy (1= extremely bad to 8= extremely good) Freiburg Personality Inventory (FPI scale): measuring stress and strain, physical complaints, health sorrows, and emotional liability Patients on SC therapy were more satisfied than those on IV therapy ($p<0.001$)						
Nicolay 2006 [28] Industry sponsorship	Short form health survey (SF-36): 8 subscales consisting of 36 items (total) querying physical function, role-physical, bodily pain, general health, vitality, social function, role-emotional, and mental health Life Quality Index (LQI): 15 statements examining respondent's perception of the impact of IgG treatment on daily activities, using a Likert scale (1= extremely bad to 7= extremely good) Group A (previous IVIg in hospital): 81% preferred SC route; 90% preferred home therapy Group B (previous IVIg at home): 69% preferred SC route; 92% preferred home therapy						
Gardulf 2004[26] Industry sponsorship	CHQ-PF50 Child Health Questionnaire-Parental Form 50: based on 15 concepts that focus on the physical and psychosocial functioning of the child and family (higher scores indicate better HRQOL) SF-36: described above LQI: described above Children and adults reported better health related QoL and treatment satisfaction after switching to SC therapy ($p < 0.05$)						

NR: not reported
RTI: respiratory tract infection (L: lower; U: upper)

APPENDIX 7: POTENTIAL USES FOR CHRONIC IG THERAPY OTHER THAN PIDS

Approved indications in Canada
B-cell chronic lymphocytic leukemia[6]
Bone marrow transplantation[6]
Secondary immunodeficiency resulting in hypogammaglobulinemia[6]
Idiopathic thrombocytopenic purpura[6]
Pediatric HIV[6]
Indications for which Ig has been used, with substantial evidence for efficacy
Anemia[6]
Aplastic anemia (pediatric)[6]
Autoimmune hemolytic anemia[54,106,107]
Dermatomyositis[6,54,101]
Erythroblastosis fetalis[54,104]
Evan's syndrome (pediatric)[6]
Gangrene[6]
Guillain-Barré syndrome[1,5,6,9,14,54,62,75,88,107-113]
Hemolytic anemia[6]
HLA-allosensitized patients awaiting renal allograft transplantation[54]
IgM paraproteinemic demyelinating neuropathy[54]
Kawasaki disease[1,2,6,9,54,62,101,107,114-117]
Leukopenia[6]
Liver function tests abnormal (pediatric)[6]
Lymphoma[6]
Megaloblastic anemia[6]
Multifocal motor neuropathy[54,62,101,108,110-113,118,119]
Multiple myeloma[6,106,117]
Myelofibrosis (pediatric)[6]
Neuropathy[6,54]
Organ transplant[6]
Refractory anemia (pediatric)[6]
Thrombocytopenia[6]
Thrombocytopenic purpura[5,6,8,9,54,55,62,101,114,116,117]
Acute myocarditis[54]
Adult-onset Still's disease[54]
Bullous pemphigoid (recalcitrant disease and those with contraindications to other therapies)[54,87,120]
Epidermolysis bullosa acquisita (rapidly progressive disease, recalcitrant disease, and those with contraindications to other therapies)[54,120]
Fetal alloimmune thrombocytopenia[8,54,104]
Grave's ophthalmopathy[54]
Inclusion body myositis[54,86]
Lambert-Eaton myasthenic syndrome[14,54,75,108,110,119]
Multiple sclerosis; relapsing-remitting MS who fail, decline, or cannot take standard immunomodulatory drug therapies[14,108,110,121]; postpartum mothers with relapsing-remitting MS[14,122]; Marburg disease[14]
Myasthenia gravis[6,54,75,106,107,110,113,119]
Neonatal alloimmune thrombocytopenia[54,62,103,106,107]
Neutropenia, immune-mediated[54,106]
Parvovirus B-19 induced anemia[54,101]
Pemphigus foliaceus (recalcitrant disease and those with contraindications to other therapies)[54,87,120]
Pemphigus vulgaris (rapidly progressive disease or recalcitrant disease)[54,120]
Polymyositis[14,54,86,106,108]

Rheumatoid arthritis and juvenile rheumatoid arthritis[54]
Stiff person syndrome[14,54,75,108,110]
Systemic lupus erythematosus[54,86,106,120]
Vasculitis (severe, resistant disease)[54,86,120]
Indications for which Ig therapy has been used, but without substantial evidence for efficacy
Acquired red cell aplasia[8]
Antiphospholipid syndrome (from 5wk to 33 wks gestation)[101,104]
Asthma[6]
Autoimmune thrombocytopenia[107,107]
Cardiomyopathy (pediatric)[6]
Chronic inflammatory demyelinating polyneuropathy (CIDP) (in combination with other immunosuppressive therapy)[5,9,14,54,62,75,88,101,107,107,110-113,119,123]
Chronic urticaria (severe, resistant disease)[120]
Coagulation disorder[6]
Demyelination[6]
Encephalitis[6]
Epidermal necrolysis[6]
Epilepsy (pediatric)[6]
Graft versus host disease[6]
Granuloma[6]
HIV (adult)[6]
Membrane proliferative glomerulonephritis[6]
Mucous membrane pemphigoid (recalcitrant disease and those with contraindications to other therapies)[87,120]
Multi system organ failure[6]
Myelitis[6]
Myopathy[6]
Myositis[6]
Necrotizing fasciitis[6]
Neoplasia[6]
Opsoclonus-myoclonus[14,108]
Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS)[14,108]
Pretibial myxedema (severe, resistant disease)[120]
Psoriasis (severe, resistant disease)[120]
Pyoderma gangrenosum (severe, resistant disease)[120]
Scleroderma (severe, resistant disease)[120]
Scleromyxedema (severe, resistant disease)[120]
Sepsis[6]
Small vessel vasculitis of the kidney (only of use in individual patients with infection or bone marrow suppression)[124]
Uveitis[6]
Vascular purpura[6]