Pharmaceutical Benefits Scheme

Post-market Review

The use of biologics in the treatment of severe chronic plaque psoriasis

Report to PBAC

Term of Reference 1

DRAFT REPORT

Contents

List of Tables

List of Figures

Abbreviations

Abbreviation	Full Name / Wording
AAD	American Academy of Dermatology
ACD	Australasian College of Dermatologists
ACR	American College of Rheumatology
AGREE	Appraisal of Guidelines for Research and Evaluation
AS	ankylosing spondylitis
BAD	British Association of Dermatology
CASPAR	The Classification Criteria for Psoriatic Arthritis
CDA	Canadian Dermatology Association
CPP	chronic plaque psoriasis
DLQI	Dermatology Life Quality Index
DoH	Department of Health
EACV	European Association for Dermatology and Venereology
EDF	European Dermatology Forum
EU	European Union
GRADE	Grading of Recommendations Assessment, Development, and Evaluation
IPC	International Psoriasis Council
MCID	Minimal clinically important difference
NICE	National Institute for Health and Care Excellence
NPF	National Psoriasis Foundation
PASI	Psoriasis Area and Severity Index
PBS	Pharmaceutical Benefits Scheme
PGA	Physician's Global Assessment
PsA	psoriatic arthritis
PUVA	psoralen and ultraviolet A
RA	rheumatoid arthritis
SCD	standard coverage days
SIGN	Scottish Intercollegiate Guidelines Network
ToR	term of reference
tx	treatment
UK	United Kingdom
US	United States

Section 1: Term of Reference (ToR) 1
Comparison of prescribing restrictions and clinical guidelines

ToR 1: Review current clinical guidelines for the treatment of severe chronic plaque psoriasis (CPP) and compare to the PBS restrictions for use of biologics in this indication from previous sponsor submissions.

1.1 Key findings for ToR 1

PBS restrictions compared with clinical guidelines

No Australian evidence-based guidelines for CPP were identified in the review; however, the review did identified two Australian consensus statements (1, 2) and numerous overseas evidence-based guidelines.

Compared with the Australian consensus and overseas guidelines, the PBS restrictions limit the use of biologics to patients with more severe CPP who have failed more prior therapies. That is, the PBS restrictions require patients:

- to have a PASI greater than 15, while the Australian consensus' recommend patients to have a PASI greater than ten (less severe CPP) and/or DLQI greater than ten (moderate or greater effect on patient quality of life). Under the Australian consensus the additional DLQI criteria may be met if there is involvement of visible areas, scalp, genitals, palms/soles, or fingernails, or if there is pruritus leading to excoriation. The PBS restrictions do not refer to DLQI, but allow treatment of patients with significant involvement of the face, palm of hand or sole of feet. UK guidelines (NICE and UK BAD) recommend biologics in patients with PASI of ten or higher and DLQI higher than ten
- to have not responded to or be unable to take at least three of the following: phototherapy, methotrexate, cyclosporin, or acitretin; versus at least two recommended in the Australian consensus guidelines.

To continue the same biologic therapy, the PBS restrictions require patients to have a greater level of response than recommended in other guidance documents. Continuation of the same biologic under the PBS requires patients to experience a reduction in PASI of 75% or more compared with their baseline level (PASI 75). Many guidance documents, including the Australian consensus, also classify patients who experience a reduction in PASI of 74-50% (lesser improvement in disease severity) with a DLQI of five or less ('small' impact on quality of life) as having an adequate response.(1, 3-5) Further, the Australian consensus outlines options other than discontinuation if adequate response is not achieved, such as adjusting the dose or adding an additional therapy.(1, 3, 6, 7)

Under the PBS, patients who fail to respond (i.e. fail to achieve a PASI 75) to three biologics must cease biologic therapy for a minimum of five years. On the other hand, no guidelines recommended a maximum number of biologics that should be trialled before discontinuing.

Most commonly recommended clinical assessment measures

Traditionally, outcome measures in psoriasis assess either disease severity or patient quality of life. Across the guidelines, the most commonly recommended measures of disease severity are PASI and Body Surface Area (BSA), and the most commonly recommended measure of patient quality of life is the Dermatology Life Quality Index (DLQI).

The PBS restrictions use PASI alone, while many guidelines (including the Australian consensus) also recommend assessing quality of life. The UK NICE guidelines, which included the most comprehensive assessment of different outcome measures, recommended PASI for assessing disease severity noting there are no other validated tools that are clearly superior. The UK NICE guidelines recommended DLQI for assessing quality of life because it is a simple practical tool that performs adequately for outcomes, such as validity, sensitivity, reliability.

Stakeholder views (Public consultation and stakeholder forum)

There was consensus amongst stakeholders that the Australian reimbursement criteria are more restrictive than clinical guidelines in Australia and internationally. Examples include:

- To qualify for a biologic on the PBS, patients must have a baseline PASI greater than 15, whereas clinical guidelines recommend biologics for people with a PASI above 10.
- Additionally, patients with psoriasis must have failed 3 out of 4 specified therapies, whereas the Australian consensus recommended that patients should be required to fail no more than 2 of 4 therapies. Many patients suffer significant side-effects from methotrexate, cyclosporine and acitretin, or are unable to access phototherapy.
- Psoriasis has a significant impact on patients' mental health and wellbeing, social interactions, work opportunities, productivity and self-confidence. Trialling prior therapies and waiting for failure to occur on prior therapies before commencing biologics can impact the patient, including their ability to work in full-time employment.
- Inclusion of a quality of life measure such as the DLQI for both initial severity assessment to initiate biologics and as an ongoing progress measurement for continuing therapy was considered very important by both patients and clinicians. This would enable patients with severe CPP, predominantly of the genitals, nails, dorsal of the hands/feet and the scalp, to access PBS-listed biologics for this condition.
- There are a number of patients with a combination of symptoms and signs of both psoriasis and psoriatic arthritis who would qualify and benefit from biologics but do not have access.
- Patients that have failed three biologics for CPP are excluded from access to PBS subsidised biologics for 5 years. Some patients who were prescribed biologics early in their availability have failed efalizumab (first PBS-listed biologic for psoriasis), which is no longer available, possibly twice, and etanercept (second PBS-listed biologic, initially restricted to 12 weeks on, minimum 12 weeks off), which is generally considered the least efficacious biologic (in the short term) for psoriasis.

1.2 ToR 1: Methodology and identification of relevant guidance

The following questions were used to assist in addressing ToR 1:

Q1. Examine whether the PBS restrictions are consistent with the clinical guidelines recommended in Australia for the treatment of severe CPP. Include consideration of the following:

a) Do the PBS restrictions reflect the clinical treatment algorithms recommended in Australian or other relevant international clinical guidelines?
b) Are the discontinuation criteria in the PBS restrictions consistent with those recommended in Australian or other relevant international clinical guidelines?
c) Are the recommendations for switching between biologic agents described in Australian or other relevant clinical guidelines? If so, are these recommendations consistent with PBS restrictions?
d) Examine the criteria in the PBS restrictions for treating patients with biologics who have: pre-existing disease (e.g. viral infection); recent vaccination; or who are pregnant. Are these criteria consistent with Australian and other relevant international clinical guidelines?

Q2. Review the most commonly recommended clinical assessment measures used to evaluate the severity of CPP or stages for disease progression.

The methodology, including the literature review, for Question 1 is described at Appendix A. In the absence of evidence-based Australian guidelines, the search also included international guidance documents. Appendix A also describes the identification of relevant guidance documents. In brief, guidance documents were assessed for inclusion using the Appraisal of Guidelines for Research and Evaluation (AGREE) II instrument.

The methodology for Question 2 is presented in Appendix C. In brief, a systematic literature search was performed to identify relevant articles about clinical outcomes in psoriasis.

1.3 Clinical guidelines for ToR 1: Question 1

1.3.1 Identification of relevant guidance documents

Nine guidance documents were identified as being relevant. This included two Australian consensus statements:

- Baker 2013, which was developed by a consensus panel comprising 12 dermatologists.(1) It was based on a European consensus statement on treatment targets,(3) which the panel adapted to take account of the Australian medical environment and prescribing patterns.
- Australasian College of Dermatologists (ACD) 2017, which was based on Baker 2013 and "adapted for use by health professionals".(2)

These are referred to throughout this review as the “Australian consensus”. The Australian consensus documents both focused on treatment targets. The only difference between them was the terminology about CPP severity, though this did not affect the treatment targets or algorithm. Both statements included two categories of disease severity with the same thresholds and treatment recommendations: Baker 2013 termed the two categories ‘mild’ and ‘moderate-to-severe’ CPP; while ACD 2017 termed them ‘mild-to-moderate’ and ‘severe’ CPP.

The other guidance documents were evidence-based guidelines from Canada, the EU, the US (American Academy of Dermatology [AAD]), UK (National Institute for Health and Care Excellence [NICE] and, separately, the British Association of Dermatology [BAD]), and consensus statements from the US (National Psoriasis Foundation [NPF]) and the EU (one on treatment optimisation and one on treatment goals). A brief overview of these guidance documents is provided in Table 1.

Table 1: Brief overview of included guidance documents

	Guidelines					Relevant consensus statements			
	Canada	**EU**	**UK NICE**	**US AAD**	**UK BAD**	**US NPF**	**Australian**	**EU: tx opti-misation**	**EU: tx goals**
Reference	(8)	(9)	(10)	(11)	(4)	(7)	(1, 2)	(6)	(3)
Primary aim / focus	Management of plaque psoriasis Update of 2009 guidelines, presented as addendum	Systemic txs only (tx goals not addressed, instead refers to 2011 consensus)	Assessment and management of psoriasis	Tx of both adult and childhood psoriasis and psoriatic arthritis.		Tx targets for plaque psoriasis. Consensus	Tx goals for psoriasis in Australia	To provide practical guidance on tx optimisa-tion & transi-tioning for moderate-to-severe CPP	To define goals for tx of plaque psoriasis with systemic therapy.
Target audience	To assist physicians in clinical decision making.	All health care professionals who treat patients with psoriasis, primarily dermatologis ts and GPs.	Healthcare professionals , commissione rs and providers, patients and their families.	Not stated	Clinical staff involved in the care of patients treated with biologics.	Not stated	Health Professionals (ACD 2017); not stated (Baker 2013)	Not stated	Not stated
Biologicals included	Infliximab Etanercept Adalimumab Golimimuab Ustekinumab	Adalimumab Etanercept Infliximab Ustekinumab	Refers to Technology Appraisal guidancs for each biologic.	Adalimumab, Etanercept, Infliximab	Infliximab Etanercept Adalimumab Ustekinumab	N/A	N/A	N/A	N/A

	Guidelines					Relevant consensus statements			
	Canada	**EU**	**UK NICE**	**US AAD**	**UK BAD**	**US NPF**	**Australian**	**EU: tx opti-misation**	**EU: tx goals**
Evidence synthesis/ summary	Literature review. Modified version of SIGN used to assign levels of evidence and grade tx recommen-dations (A, B, C, D). Grade was applied to the level of evidence, with ‘‘considered judgment’’ allowing some flexibility.	Comprehen-sive, systematic literature search; Evidence summarized using the GRADE system	Comprehen-sive, systematic literature search; Evidence summarized using the GRADE system	Literature search; Evidence evaluated using the Strength of Recommen-dation Taxonomy developed by editors of the US family medicine and primary care journals. Evidence was graded using a 3-point scale.	Literature search. Evidence was summarised using the levels of evidence and grades of recommenda-tion from SIGN.	Literature review, (2) pre-Delphi question selection and input from general dermatolo-gists and patients, and (3) 4 Delphi rounds.	Baker 2013: Literature review; panel “critically examined available evidence-based tx goals”. ACD 2017: Endorsed by ACD Board. Process not stated.	Literature review (where possible) and Dephi rounds. Evidence graded using the Oxford Centre for Evidence-Based Medicine classification levels.	N/A

	Guidelines					Relevant consensus statements			
	Canada	**EU**	**UK NICE**	**US AAD**	**UK BAD**	**US NPF**	**Australian**	**EU: tx opti-misation**	**EU: tx goals**
Basis for recommen-dations	Guidelines Committee of 16 Canadian dermatolog-ists. Reviewed by the wider medical community and the Therapeutics Committee of the CDA, then formally endorsed by the CDA.	Based on the evidence, recommen-dations were formulated and consented by an expert panel of dermatolo-gists a rheu-matologist and 2 patient representa-tives. They were officially nominated by the EDF, EACV, IPC.	Based on the Guideline Development Group's interpreta-tion of evidence, taking into account benefits, harms and costs. The Guideline Development Group comprised professional group members & consumer representa-tives.	Clinical recommen-dations were developed based on the best available evidence, which was ranked using 3-point system	Recommen-dations were developed for implementa-tion in the National Health Service using a process of considered judgment based on the evidence and an awareness of the European product licence of the various txs.	Consensus after 4 Delphi rounds. Consensus group were 25 members of the NPF board and other psoriasis experts. Conducted by the NPF.	Baker 2013: A question-naire was developed with questions related to the content of Mrowietz *et al* 2011. Following discussion & debate, recom-mended tx goals were determined.	Modified Delphi procedure consisting of several stages and involving 147 dermatolo-gists.	A consensus conference & Delphi technique were used. The consensus group consisted of 19 dermatol-ogists. Consensus among ≥17 of 19 experts was regarded ''agreement'' /strong consensus.
AGREE II score: 1 to 7 [b]	7	7	7	5	6	4	4	4	4

AAD = American Academy of Dermatology; AGREE = Appraisal of Guidelines for Research and Evaluation; BAD = British Association of Dermatology; CDA = Canadian Dermatology Association; CPP = chronic plaque psoriasis; EACV = European Association for Dermatology and Venereology; EDF = European Dermatology Forum; EU = European Union; GPs = general practitioners GRADE = Grading of Recommendations Assessment, Development, and Evaluation; IPC =International Psoriasis Council; N/A = not available; NICE = National Institute for Health and Care Excellence; NPF = National Psoriasis Foundation; SIGN = Scottish Intercollegiate Guidelines Network; tx = treatment; TOR = term of reference; UK = United Kingdom; US = United States

[a] Also included alefacept and efalizumab.

[b] Where 1 is the lowest and 7 is the highest score

1.3.2 Summary of clinical guidance and comparison to PBS restrictions

PBS restrictions

Under the PBS, biologics for CPP are restricted to patients with a PASI greater than 15 who have not responded to or who are unable to take at least three of the following: phototherapy, methotrexate, cyclosporin, and acitretin.

To continue PBS-subsidised use of a particular biologic therapy, patients must experience a reduction in PASI score of 75% or more compared with their baseline level (PASI 75). Patients who fail to respond to three biologics are considered to have completed that treatment cycle and must cease PBS-subsidised therapy. A new biological treatment cycle may be recommenced after a minimum of five years has elapsed.

PBS restrictions compared with clinical guidelines

Table 2 compares the PBS restrictions for biologics in CPP with relevant guidance (note only guidance with relevant recommendations are included). Further details, including the treatment algorithm proposed by the Australian consensus, are presented in Appendix B.

Number of prior therapies:

The PBS restrictions require patients to have failed to achieve an adequate response to, or be contraindicated or intolerant to at least three of the following four treatments: phototherapy, methotrexate, cyclosporin, acitretin. As outlined in Table 2, compared with the PBS restriction:

- The Australian consensus statement recommended fewer prior therapies (at least two of the same four prior therapies above) could be used prior to initiating biologics.
- The EU guidelines, UK NICE Technology Appraisal Guidance and UK BAD guidelines do not state a specific number of prior therapies that should be trialled, but more generally state that these therapies must have been failed, contraindicated, or not tolerated.(4, 5, 9) Similarly, the US AAD guidance does not provide specific recommendations about when to use biologic versus other systemic agents. However, it notes that methotrexate, acitretin and cyclosporin have well-known toxicity profiles, are given orally and are less expensive than biologics. It notes that biologics are additional options that are potentially less toxic to the liver, kidneys, and bone marrow and are not teratogenic.(18)
- The Canadian guidelines do not recommend trialling other systemic agents or phototherapy prior to biologic therapies, stating that there is no clinical reason to reserve biologics for second-line systemic use noting biologics have less severe toxicities. It recommend acitretin, cyclosporin, or methotrexate to ameliorate moderate to severe plaque psoriasis; while biologicals or phototherapy are recommended to achieve complete control.(19)

Intolerance/contraindications to prior therapies

To determine whether a patient is contraindicated to methotrexate, cyclosporin or acitretin, the PBS restrictions follow the TGA-approved Product Information. To determine 'intolerance', the toxicity criteria are outlined on the Department of Human Services website and are generally based on the National Institutes of Health common toxicity criteria grade 2 or higher, depending on the adverse event and the agent. None of the

guidelines or consensus statements outline specific contraindications or intolerance levels that should be met. However, some guidelines are less restrictive than the PBS, with the UK BAD guidelines classifying the risk of developing toxicity as intolerance.

For phototherapy, many of the guidance documents noted that access can be an issue, and that cumulative exposure to UVA should be limited (e.g. Canadian guidelines); however, it was noted by the reference group that narrowband UVB is mostly used in Australia not UVA.

Prior therapies: Acitretin and cyclosporin

The PBS restrictions require that patients have failed, be contraindicated to, or unable to tolerate acitretin and/or cyclosporin. However, other guidelines do not recommend acitretin monotherapy or long-term use of cyclosporin.(9, 19)

- Acitretin monotherapy: The Canadian guidelines noted that there is little evidence for the benefit of acitretin monotherapy in plaque psoriasis (but noted there is evidence for use in combination with topical calcipotriol or phototherapies). Similarly, the EU guidelines stated it could not make a recommendation for or against acitretin monotherapy based on the available evidence.
- Long term use of cyclosporin: The Canadian guidelines recommended that cyclosporin should be reserved for intermittent control and ordinarily should not be used for periods greater than 12 weeks (Grade B recommendation). The EU guidelines suggest use of cyclosporin for a maximum of two years. If a longer-term treatment is needed, they suggest consultation with a nephrologist (consensus based on expert opinion). Similarly, the EU consensus on treatment optimisation considered that cyclosporin should only be used short term to induce a clinical response. It noted that cyclosporin is generally used intermittently with one or several courses over three to six months. In exceptional cases, where no other treatment options are available, cyclosporin may be given for longer than two years but caution is advised because of the risk of renal toxicity, arterial hypertension and skin cancer.

CPP severity required to be eligible for biologics:

Under the PBS, biologics are restricted to patients with more severe CPP than recommended in guidance. Further, many of the guidance documents also take quality of life into account (the specific outcome measures are discussed in Question 2).

The PBS restrictions require patients to have:

- PASI greater than 15 (This is termed “severe” CPP in the PBS restriction, though terminology relating to mild, moderate and severe CPP varies between guidelines); or
- CPP of the face, palm of hand or sole of foot, with two or more of the PASI symptom sub-scores (erythema, scale and duration) rated as ‘severe’ or ‘very severe’; or 30% or more of the area is affected.

As PASI incorporates body surface area, more than 20% of a patient’s body surface area would need to be affected to achieve a PASI greater than 15. Thus, patients with severe disease localised to a small area would only be eligible under the latter criterion (i.e. only if face, palm of hand or sole of foot is involved).

As outlined in Table 2, this is more restrictive than all guidance documents identified:

- The Australian consensus recommends biologics in patients with PASI greater than 10 and/or DLQI greater than 10 (i.e. large effect of quality of life). The Australian consensus notes that quality of life may be impaired (high DLQI) in less severe disease (low PASI) in patients who have involvement of: visible areas, scalp, genitals, palms/soles, two or more fingernails, and/or pruritus leading to excoriation. The PBS restrictions do not include patients with involvement of genitals, or two or more fingernails, unless other areas were also affected.
- The UK NICE and UK BAD guidelines use a less severe PASI threshold than the PBS restriction, but require that patients also have impeded health related quality of life. They recommend biologics in patients with PASI of ten or higher and DLQI higher than ten (except infliximab, for which UK NICE uses higher thresholds).
    - The UK BAD guidance stated that in exceptional circumstances patients with severe disease may fall outside this definition but should be considered for treatment. Examples included disease affecting high-impact sites with associated significant functional or psychological morbidity such as psoriasis affecting the genitalia, hands, feet, head and neck.
- The Canadian guidelines do not specify numerical cut-offs for initiating biologics stating, "they fail to reflect patients' actual burden of disease. In clinical practice, more patient-centred standards are needed." The definition of severe CPP in the Canadian guidelines is "disease that cannot be, or would not be expected to be, satisfactorily controlled by topical therapy and that causes severe degradation of the patient's quality of life."

For CPP of the face, a palm of a hand or the sole of a foot, the PBS restriction requires that: two or more of the PASI symptom sub-scores (i.e. erythema, scale and duration) be rated as 'severe' or 'very severe'; or 30% or more of the area is affected. The Australian consensus considered this was appropriate and could be combined with the proposed DLQI assessment.

Table 2 Treatment algorithms for use of biologics in CPP: PBS versus other guidance

PBS restrictions	Evidence-based Guidelines			Consensus
	Canada (8)	EU (9)	UK NICE Technology appraisals and UK BAD (10) (12-17), (4)	Australian (1, 2)
Second line treatments				
Phototherapy, methotrexate, cyclosporin, acitretin	To ameliorate CPP: methotrexate cyclosporin, or acitretin; For complete control: biologicals or phototherapy.	Phototherapy methotrexate, cyclosporin (short course), fumaric acid esters. (Not acitretin monotherapy)	PUVA, methotrexate, cyclosporin, acitretin	Phototherapy, methotrexate, cyclosporin, acitretin.
Biologics - prior treatments				
≥ 3 of the above 4 therapies failed, contraindicated or intolerant	No clinical reason to reserve the biologics for after second-line use.	Use if above therapies were inadequate in response or contraindicated or not tolerated.[a]	Use if above therapies were inadequate in response or contraindicated or not tolerated. [a] UK BAD included risk of toxicity or unstable life-threatening CPP.	≥ 2 of 4 therapies inadequate in response or contraindicated.
Strength of above recommendation				
	Not a formal recommendation. Referenced a 2004 consensus of the Canadian Psoriasis Expert Panel.	Strong recommendation, Evidence and consensus based with strong consensus	UK NICE: From Technology appraisal guidance (from the Appraisal Committee, who generally assessed randomised, controlled trial evidence). UK BAD: Strength of recommendation D; level of evidence 3, and formal consensus	The consensus group proposed this "as reasonable and best practice" (no citation provided).
Severity assessment criteria				
PASI >15 (termed "severe" CPP)	Numerical cut-offs not specified as they don't reflect actual burden of disease. More patient-centered standards needed.	-	PASI ≥10 and DLQI >10 [b] UK BAD also included BSA ≥10% if PASI not applicable, and allowed exemptions in exceptional circumstances.[c]	PASI >10 and/or DLQI >10 [d] (termed "severe" CPP in ACD 2017, but "moderate-to-severe" in Baker 2013).

PBS restrictions	Evidence-based Guidelines			Consensus
	Canada (8)	**EU (9)**	**UK NICE Technology appraisals and UK BAD (10) (12-17), (4)**	**Australian (1, 2)**
Strength of above recommendation				
-	"Key Point", referenced to NPF consensus statements and position papers.	N/A (referenced EU tx goals consensus)	UK NICE: from Technology Appraisal Guidance. UK BAD: Strength of recommendation D; level of evidence 3 [e]	Consensus
CPP of the face, palm of hand or sole of foot				
≥ 2 of 3 PASI symptom sub-scores rated as 'severe' or 'very severe' or ≥ 30% of area affected	1st-line: topical 2nd-line: acitretin, methotrexate, infliximab, adalimumab, ustekinumab, cyclosporin	-	UK NICE: may be more likely to be included given the lower PASI threshold. UK BAD: covered in exceptional circumstances.	Considered the PBS definition for severity was appropriate and could be combined with the proposed DLQI assessment.

ACD = Australasian College of Dermatologists; BAD = British Association of Dermatologists; BSA = body surface area; CPP = chronic plaque psoriasis; DLQI = Dermatology Life Quality Index; EU = European Union; NICE = National Institute for Health and Care Excellence; PBS = Pharmaceutical Benefits Scheme; PASI = Psoriasis Area and Severity Index; PUVA = psoralen and ultraviolet A; UK = United Kingdom

[a] Number of prior therapies that should be trialled was not stated.

[b] Except infliximab which is PASI ≥20 and DLQI >18.

[c] UK BAD guidelines also state: In exceptional circumstances patients with severe disease may fall outside this definition but should be considered for treatment, e.g. disease affecting high-impact sites with associated significant functional or psychological morbidity such as acral psoriasis, or psoriasis affecting the genitalia, hands, feet, head and neck.

[d] Upgrade mild disease to moderate-to-severe if there is: major involvement of visible areas or the scalp, involvement of genitals, onycholysis or onychodystrophy of at least two fingernails, presence of itch leading to excoriation.

[e] Except ustekinumab as second-line: only a weak consensus of the definition of second line.

Rationale for PBS restrictions

Efalizumab was the first biologic listed for CPP (but was withdrawn from the PBS in 2009). The Public Summary Document states:

"The PBAC recommended that, to achieve the dual objective of identifying severe refractory psoriasis, the restrictions include the requirement for a baseline PASI score of greater than 15 and that this must be assessed following treatment with each of the three nominated therapies (methotrexate, cyclosporin and phototherapy) with dosage regimens and minimum durations as included in the requested restriction." (November 2005, Efalizumab Public Summary Document).

The key clinical trial presented was conducted in patients who were unresponsive, intolerant or contraindicated to at least two systemic therapies and had a baseline PASI greater than 15 (November 2005, Efalizumab Public Summary Document).

The next biologic that was listed for use in CPP was etanercept. It was recommended at the March 2006 PBAC meeting for severe refractory CPP on a cost-minimisation basis with efalizumab. The PBAC recommended that the restriction be closely aligned to the ratified restriction for efalizumab. Further, the PBAC considered that interchangeability arrangements with efalizumab should be developed similar to those for rheumatoid arthritis and ankylosing spondylitis, and that a 5 year exclusion period should apply following failure to demonstrate a response. (March 2006, Etanercept Public Summary Document).

Other subsequently listed biologics for CPP were recommended on the basis that the restrictions were consistent with those already listed (dosing and the initiation periods were amended where appropriate). Thus, the PBS restrictions around prior therapies and PASI thresholds are based on those proposed for efalizumab and etanercept.

There has also been a request to increase the number of biologics that a patient can use in a treatment cycle from three to four, but this was not recommended:

"The PBAC considered that it would be appropriate for the number of bDMARD therapies that a patient may trial per treatment cycle remain at three as no data directly supportive of changing to four therapies was presented in the submission and the sponsor had accepted that the current arrangements in its pre-PBAC response (p.1). The PBAC noted that keeping the maximum number of treatments at three would still allow a patient to have tried and failed one biological agent from each available class of bDMARD, including secukinumab, before the treatment cycle is over. Retaining the number of therapies attempted at three would also ensure that the listing would truly be in line with a cost-minimisation recommendation." (Paragraph 7.9, Secukinumab Public Summary Document, March 2015).

Previous PBAC consideration of use of biologics in moderate CPP

In March 2013, the PBAC considered adalimumab for listing in moderate CPP (it was already listed for severe CPP).

The submission originally requested listing for use in adult patients with moderate to severe chronic plaque psoriasis, defined by a PASI or DLQI greater than 10, (but a PASI of 15 or less as these patients would be covered by the existing restriction), who have failed to respond to at least two non-biologic therapies (instead of three). This was consistent with the

Australian consensus. However, during the evaluation/consideration process, this was amended to remove DLQI and the requirement for fewer prior therapies:

"The PBAC noted the advice in the submission's Pre-Sub-Committee Response (PSCR) that the sponsor consented to the evaluator's recommendation of a listing for moderate to severe disease consistent with the current listing for severe disease, with patients being required to have failed to respond to treatment with 3 of 4 prior therapies, and assessment of disease severity on PASI alone." (Section 4, Adalimumab Public Summary Document, March 2013).

The PBAC rejected the submission on the basis of highly uncertain cost-effectiveness. Other relevant points (from the Adalimumab Public Summary Document March 2013) included:

- "With regard to safety, the PBAC was particularly concerned with the use of adalimumab (and monoclonal antibodies in general) in larger patient populations to treat milder forms of disease, albeit with high health distress, insofar as it increases exposure of patients to the adverse effects associated with use of these agents, particularly infection and malignancy."
- "The PBAC considered that there was a risk that adalimumab would be used in a proportion of patients with mild disease (i.e., PASI < 10), since determination of a PASI score is to some extent subjective. Furthermore, the PBAC noted that a proportion of patients with moderate psoriasis might be currently receiving PBS subsidised adalimumab under the severe disease restriction. The PBAC requested a review of the use of adalimumab in patients with moderate disease." (Adalimumab Public Summary Document, March 2013).

The subsequent DUSC report acknowledged that there may be use of biologics for the treatment of moderate psoriasis through the PBS, although this cannot be ascertained from prescription data. The DUSC report also noted that "In addition to [the Australian consensus] that considers a wider group of patients are suitable for biological therapies than currently subsidised, the DUSC noted all four bDMARDs have clinical trial evidence and TGA registration for the broader moderate to severe psoriasis indication. The DUSC also noted the NICE guidance recommend use in moderate to severe disease [PASI of ten or higher and DLQI of higher than ten]. The DUSC considered that use outside the PBS restriction to patients with less severe disease might be occurring, while some patients with severe refractory disease remain unable to access bDMARDs."

1.3.3 Discontinuation/continuation in PBS restrictions compared to clinical guidelines

Table 3 below compares the PBS continuation criteria with recommendations from relevant guidance documents. A more detailed table is provided in Appendix B.

Adequate response and continuation of the same biologic agent

To continue biologics under the PBS, patients must experience a change in PASI of 75% or more compared with the baseline level.

- Many guidance documents also recommend continuation for patients who have a reduction in PASI of 74-50% and a DLQI of five or less (i.e. lower disease severity but

with impaired quality of life). These guidance documents are the UK (NICE Technology appraisal guidance), UK (BAD) and the Australian and the EU consensus on treatment goals.

- The Australian consensus' noted that patients may still experience impaired quality of life (DLQI of five or more), even with a reduction in PASI of 75% or higher. For example this may occur if there is involvement of a visible site, genital, palmoplantar, nail involvement or pruritus or response is discordant with patient's expectations. In this case, the document stated it should be up to the physician's discretion whether to continue, modify or change therapy.
- The Canadian guidelines recommend that treatment success should rely on patient satisfaction and health related quality of life in addition to traditional objective indicators of disease response. It also notes that amelioration may be an adequate treatment goal for some patients, while full clearance represents an appropriate goal for many patients.

If adequate response is not achieved

Under the PBS, if an adequate response is not achieved, the biologic must be discontinued. On the other hand, the consensus statements outline other options including adjusting the dose, adding another therapy (combination therapy) or switching to another therapy. The evidence-based guidelines do not make specific recommendations in this regard, although the Canadian guidelines discuss instances where, in weak responders, response may improve by maintaining therapy or increasing the dose. The UK NICE guidelines state that for adults in whom there is an inadequate response to a second biological drug, supra-specialist advice should be sought from a clinician with expertise in biological therapy.

Under the PBS, patients who fail to respond to three biologics are considered to have completed that treatment cycle and must cease PBS-subsidised therapy. A new biological treatment cycle may be recommenced after a minimum of five years has elapsed. On the other hand, no guidelines recommended a maximum number of biologics that should be trialled before discontinuing biologic therapy.

Table 3 Continuation and discontinuation criteria for biologics in CPP

PBS restrictions	Evidence-based Guidelines		Consensus	
	Canada (8)	UK NICE (10)	Australian [a (1, 2)]	EU consensus tx goals (3)
To continue with the same biologic regimen unchanged (all indicators are versus baseline)				
ΔPASI ≥ 75% [b]	Pt satisfaction, HRQoL and "traditional objective indicators of response".	ΔPASI ≥ 75%; or ΔPASI 74-50% and DLQI ≤5.	Same as UK NICE (but noted if ΔPASI ≤ 75% but DLQI ≥ 5: use physician assessment whether to continue, modify or change tx[c])	Same as UK NICE
If adequate response not achieved (i.e. responses above are not achieved)				
Discontinue. If inadequate response to 3 biologics, cease all biologics for 5 years.		Discontinue drug if above response not achieved. If inadequate response to a 2nd biological drug, seek supra-specialist advice.	Modify regimen.	Modify regimen. Modification strategies: adjust dose; add another tx (combination tx); switch tx.

CPP = chronic plaque psoriasis; DLQI = Dermatology Life Quality Index; EU = European Union; HRQoL = health related quality of life; NICE = National Institute for Health and Care Excellence; PASI = Psoriasis Area and Severity Index; tx = treatment; UK = United Kingdom

[a] Based on text and the treatment algorithm diagram.

[b] For face, palm of hand and sole of foot: A reduction in all three PASI subscores to 'slight' or 'none' or ≥75% reduction in the area affected. The Australian consensus considered the PBS definitions were appropriate and could be combined with the proposed DLQI assessment.

[c] Noted ΔPASI ≥75 but DLQI ≥ 5 may occur if the psoriasis is on a visible site, genital, palmoplantar, nail involvement or pruritus or response is discordant with patient's expectations.

Face, palm of hand, sole of foot

For PBS continuation, patients with psoriasis of the face, palm of hand or sole of foot must achieve a reduction in all three PASI subscores to 'slight' or 'none' (the sub-scores are erythema, thickness and scaling) or ≥75% reduction in the area affected. The Australian consensus considered the PBS definitions were appropriate and could be combined with the proposed DLQI assessment for inclusion in the Australian treatment goal framework.

1.3.4 Switching - changing between biologic therapies

Under the PBS, patients can change to a different biological therapy as long as they have not already failed or ceased to respond to that particular agent or three other biological agents within a five-year treatment cycle. Switching can be for any reason, and is not limited to a lack of response. If a patient is switching despite having achieved an adequate response, then a demonstration of response must be submitted within one month to avoid appearing to fail the therapy.

The ability to switch between biologics is consistent with guideline recommendations about individualising therapies, taking into account the risks and benefits and the differing adverse effect profiles of the biologics. For example, the Australian consensus group felt that patient preferences regarding the type of treatment and their views relating to treatment success or failure should be taken into consideration when making treatment decisions.

1.3.5 PBS restrictions for patients who have specific needs

Patients under the age of 18 years

Etanercept is the only biologic that is PBS-listed for the treatment of CPP in patients aged under 18 years. This aligns with the Canadian, US AAD and UK BAD guidelines, which outline that etanercept is the best-studied biologic for paediatric psoriasis. Nice Technology appraisal guidance recommends adalimumab as an option for patients aged four years and older, etanercept for patients aged six years and older and ustekinumab for patients aged 12 years and older, neither adalimumab nor ustekinumab have requested PBS listing for these age categories.

Pregnancy

The PBS restrictions do not include specific criteria around use of biologics in pregnancy, but do allow pregnant women to forgo the requirement to have failed methotrexate and acitretin, as they are contraindicated (due to teratogenicity) during pregnancy per the TGA-approved Product Information. This aligns with clinical guidelines.

Other than this, the PBS restrictions do not specifically restrict (nor enable) use of biologics in pregnancy. This aligns with the Canadian and US AAD guidelines, which recommend that prescribers assess the risks and benefits. The Canadian and US AAD guidelines note that the US Food and Drug Administration classify adalimumab, etanercept and infliximab as pregnancy 'Category B' (i.e. animal reproduction studies have failed to demonstrate a risk to the foetus and there are no adequate and well-controlled studies in pregnant women"). Both guidelines recommend that prescribers assess the risks and benefits and, if required, recommend that these drugs be used with caution. (Note that the TGA pregnancy classifications differ substantially. The definitions of the categories differ as does the category assigned: adalimumab, infliximab, ixekizumab and secukinumab are pregnancy 'Category C'; etanercept is Category D; ustekinumab is Category B1.)

Note that under the PBS, if patients temporarily cease biologic therapy - for example due to pregnancy - a demonstration of response to the biologic must be submitted within one month of stopping treatment to enable them to restart without been counted as a fail to therapy. Thus if patients were to temporarily cease biologics due to pregnancy, they could re-start as long as this demonstration of response had been submitted.

Use of biologics to treat CPP in other special populations and circumstances

The PBS restrictions for biologics do not outline specific criteria around pre-existing disease (e.g. viral infection), recent vaccination or use in patients who are pregnant. This somewhat aligns with the Canadian guidelines which state that "large, controlled clinical studies are almost unknown in special populations with psoriasis, so physicians must rely largely on the case literature and clinical judgment when treating these patients."(19)

The Canadian, US AAD and UK BAD guidelines (which are the only guidelines that provide specific discussion on special populations and circumstances) outline that:

- The use of live or live-attenuated vaccines is not recommended while on biologics. The US AAD guidelines recommend that patients receive standard vaccinations prior to commencing biologic therapy.
- Patients should be screened for hepatitis B and C prior to commencing biologics due to the risk of virus re-activation. The Canadian guidelines recommend that HBV-

positive patients with inactive disease receive a course of antiviral therapy starting two to four weeks before the biologic, followed by close monitoring of liver function and viral load while on the biologic.

1.4 Summary of outcomes for ToR 1: Question 2

This section summarises the outcome measures that are commonly recommended in guidance (focusing on the Australian consensus statement and the evidence-based guidelines) and the findings of the literature review on outcome measures.

1.4.1 Outcomes commonly recommended in guidance

Outcomes recommended in guidance

Table 4 outlines the outcome measures that are recommended or noted in the guidance. A tick indicates that the outcome was recommended or provided as an example of an outcome that could be used. A cross indicates an outcome that was specifically not recommended. Further information about the rationale for selection of specific measures is outlined in Appendix B with key points summarised in the text below. As shown, the most commonly recommended clinical assessment measures are the PASI, DLQI and Body Surface Area (BSA). Note that an assessment of BSA is included in the PASI.

Table 4: Outcome measures recommended or noted in guidelines

		Evidence-based guidelines					Consensus statements		
	PBS	**Canada (8)**	**EU [a] (9)**	**UK NICE [b] (10)**	**US AAD (11)**	**UK BAD (4)**	**US NPF (7)**	**Australian (1, 2)**	**EU tx goals (3)**
PASI	✓		✓	✓	x [c]	✓	x	✓	✓
DLQI	x	✓	✓	✓		✓	x	✓	✓
BSA	x		✓	✓	✓		✓	x [d]	✓
PGA	x		✓	✓	✓		x	x	x
Other	Face, hands, feet	PDI, DLQI, DQOLS, SF-36, or PSA (HRQoL should be central to psoriasis management).	Skindex	Patient's Global Assessment					
Children	PASI			PASI & BSA are not validated in children				CDLQI	

AAD = American Academy of Dermatology; BAD = British Association of Dermatology; BSA = body surface area; CDLQI = Children's Dermatology Life Quality Index; DLQI = Dermatology Life Quality Index; DQOLS = Dermatology Quality-of-Life Scales; EU = European Union; HRQoL = Health-Related Quality of Life; NICE = National Institute for Health and Care Excellence; NPF = National Psoriasis Foundation; PASI = Psoriasis Area and Severity Index; PBS = Pharmaceutical Benefits Scheme; PDI = Psoriasis Disability Index; PGA = Physician's Global Assessment; PSA Scale = Psoriatic Arthritis Scale; SF-36 = Short Form Health Survey; tx = treatment; UK = United Kingdom; US = United States

[a] The EU guidelines recommend objective assessment of the disease (using instruments such as PASI, BSA, PGA) and assessment of HRQoL (e.g. using DLQI or Skindex) before and during treatment.

[b] The UK (NICE) guidelines state that in specialist settings, a validated tool should be used to assess severity and the impact on physical, psychological and social wellbeing, e.g. DLQI (or CDLQI for younger people).In any healthcare setting, record: PGA; the patient's assessment of current disease severity, for example, using the static Patient's Global Assessment; the BSA; any involvement of nails, high-impact and difficult-to-treat sites.

[c] Noted PASI is commonly used in trials, but the authors considered it to be less sensitive in patients with lower BSA involvement (<10%). Also stated that PASI was rarely used in clinical practice.

[d] Noted BSA was included in the EU treatment goals consensus but this was not included in the Australian consensus because it is not routinely used in Australian clinical practice and adds little clinical value to PASI.

PBS versus Australian guidelines

The PBS restrictions use only PASI (a disease severity measure) to determine eligibility and treatment success. However, many guidelines recommend measurement of both disease severity and quality of life. For example, the EU guidelines state that both were incorporated in order to integrate both the dermatologist's and the patient's judgement.(9)

The Australian consensus recommends use of both PASI and DLQI.(1) The Australian consensus selected DLQI to assess health related quality of life because it is: (i) supported by strong evidence; (ii) the most commonly used worldwide; and (iii) valid and easy to use. The group considered that DLQI would identify a group who might otherwise be considered to have mild disease, while also giving some indication of patient satisfaction with treatment.(1) BSA was not included in the Australian consensus because it is not routinely used in Australian clinical practice and was considered to add little clinical value to the PASI score.(4)

The PBS restriction uses PASI in children, while other guidelines state that PASI has not been validated for use in children and young adults. (5) The only outcome measure that appears to be validated or recommended in children is the Children's DLQI (which measures quality of life).

Evidence-based guidelines

Many of the evidence-based guidelines outline a range of validated outcome measures that could be used, rather than nominating one or two specific instruments. For example, the EU and UK NICE guidelines recommend objective assessment of disease severity and assessment of health related quality of life, using "validated measures". The EU guidelines outline a list of validated measures, while the UK NICE guidelines express a preference for particular measures in particular settings. *This likely reflects that overall, there is limited reliable clinical evidence comparing the various measures.* For example, the Canadian guidelines note that there are no large randomised controlled studies to evaluate the comparative utility of different measures in clinical practice. *Further, none of the measures appear perfect. Each has strengths and limitations that render its use more or less appropriate in specific circumstances.*

Overall, the guidance acknowledged the overarching limitations of the measures. The EU guidelines stated that instruments like PASI, DLQI and Skindex-25 do not "capture the seriousness of psoriasis as experienced by those who have the disease". They focus on immediate, current or very recent (over the last week) acute symptoms and circumstances, despite it being a chronic disease.

On the other hand, many of the consensus documents selected measures that are commonly used, rather than what is evidence-based.

UK NICE recommendations

Of all the guidelines, the UK NICE guidelines included the most comprehensive literature review and assessment of the validity and reliability of tools for measuring psoriasis. The guidelines committee considered that, when recommending specific tools, the following outcomes should be prioritised: validity, internal consistency, intra-rater and inter-rater reliability, practicality and sensitivity to change. The guidelines committee concluded that the "preferred tools" for use in specialist settings are the PASI and DLQI (the latter could be used in non-specialist settings if practical).

- PASI was chosen for use in specialist settings because: it performed at least at an adequate level for the prioritised outcomes; healthcare professionals in specialist settings are already trained in its use and interpretation; the majority of clinical trials use PASI and therefore treatment effects are quantified using this tool; and although the PASI has limitations, there are no other validated tools that are clearly superior at present.
- DLQI was chosen because it is a simple, practical tool that performed at least adequately in the prioritised outcomes, and because there was an absence of high quality evidence that other tools were better. However, the limitations of the DLQI were acknowledged including inadequate capture of the psychological impact of psoriasis (e.g. mood, wellbeing and coping). The guidelines noted that Skindex-17 may have advantages in these regards but, at the time that the guidelines were

developed there was very limited evidence of its validity and reliability in people with psoriasis.

- An update to the UK NICE guidelines (published in 2014) noted that the Simplified Psoriasis Index (SPI), a tool that measures both disease severity and patient impacts, appears to be valid and reliable. The update stated that SPI appears to provide a simpler and more comprehensive means of psoriasis assessment but further validation is needed. (5, 10)

Guidelines that do not recommend PASI

Two evidence-based guidelines do not recommend PASI:

- The US AAD guideline, instead recommends BSA or the Physician's Global Assessment (PGA). It notes PASI is commonly used in trials, but the authors considered it to be less sensitive in patients with lower BSA involvement (<10%). It also states that PASI was rarely used in clinical practice. Similarly, the US NPF consensus statement (not an evidence-based guideline), stated that BSA was the most preferred instrument. General dermatologists stated that BSA was the most familiar and most widely used measure in clinical practice in the US.(7)
- The Canadian guidelines did not recommend any outcomes that measure disease severity, but instead recommended that quality of life factors should be central to the long-term management of psoriasis (Level of Evidence 4, Grade D). It recommended that quality of life measures such as the Psoriasis Disability Index (PDI), DLQI, Dermatology Quality of Life Scales (DQOLS), Short Form Health Survey (SF-36), or the Psoriatic Arthritis Scale (PSA) should be employed when practical.

1.4.2 Literature review of PASI and DLQI

The results of the literature review of the PASI, DLQI, Skindex and the SPI instruments are summarised in Appendix D. The key findings are outlined below.

PASI

The key benefits of PASI identified in the guidelines and the literature review are that:

- It is the most commonly used psoriasis assessment tool in Australia. (1)
- It is the most commonly used outcome in clinical trials and thus the treatment effects are quantified using this tool.
- It is the most extensively validated score (20) (21) thus its limitations are known.
- It is generally considered to be reproducible with high intra-rater reliability and moderate to high inter-rater reliability, particularly if measured in specialist settings. (5, 20)

The key limitations of PASI are that:

- It does not incorporate the patient's perspective, including pain, itch and pigmentation which may impact on quality of life.
- It lacks sensitivity to disease that affects a small area of the body (less than 10% BSA), which can have a disproportionately high impact on functional or psychosocial well-being. The PBS uses a specific instrument (which appears to be an adaptation

of the PASI) for CPP of the face, hands and feet. However this does not capture disease that affects other small areas such as the genitals or nails.

- Few studies have reviewed the validity and reliability of PASI at specific body sites and in different phenotypes of psoriasis.(5) This limitation also applies to all the other tools used to assess psoriasis severity.
- It is not validated in children or young adults.
- There is no consensus on the interpretation or clinical meaning of changes in PASI (e.g. there is no consensus as to what score represents severe disease).
- It is non-linear and lacks sensitivity at the lower end of its range and the upper half of its range is redundant. (21) (20)
- One review considered that PASI had only moderate content validity because plaque elevation was not given a higher weight, despite the review authors considering this to be the most significant clinical sign of psoriasis. (20)
- It is longer and more complicated to assess than other measures, such as the Physician's Global Assessment (PGA). Various authors and guidelines have suggested that PGA is better suited than PASI in non-specialist settings. (5, 22)

Correlation between PASI and other disease severity measures

Given the limitations of PASI, several other measures have been developed to assess psoriasis disease severity. Two that are commonly used are the PGA and the Lattice System-PGA (LS-PGA). PASI has been found to be well correlated with these measures.[5, 23, 24] As such, the authors of one systematic review concluded that the two tools (PASI and PGA) are substantially redundant and either alone is sufficient for assessing psoriasis severity in patients with moderate to severe disease [22]. Note that the evidence of correlation between PASI and LS-PGA is more limited than between PASI and PGA (refer to Appendix D).

As discussed later, PASI generally correlates well with other physician-based assessments, but not with health related quality of life measures.

PASI: balance of benefits and limitations

As discussed earlier, the UK NICE guidelines committee concluded that although the PASI has limitations, there are no other validated tools that are clearly superior at present.(5) A NICE evidence update, published in November 2014, did not find any evidence to change this conclusion. (10)

Similarly, the authors of one review article concluded: "When choosing a measure, it is important to determine the most needed features, for example, good responsiveness or sensitivity in mild disease. It may be necessary to combine two or more scores to satisfy all needs. For example, PASI may not be particularly sensitive for mild disease, but it may be outstanding for a study in which patients have severe disease. It also provides the advantage of a large base of studies in which it has been used. Another instrument may have some characteristics that are better, but this may not outweigh the benefit of being able to compare with the existing database of studies that used PASI." (20)

Overall, many of the limitations of PASI may not be relevant for assessing psoriasis severity in the context of PBS eligibility for biologics, including:

- *While PASI is complex and its reliability depends on physician experience, PBS eligibility requires that the patient be treated by a dermatologist.*

- *While it does not incorporate the patient perspective, it could be used in conjunction with DLQI.*
- *While it lacks sensitivity at the lower end of its range, biologics are not PBS-listed for mild disease.*

DLQI

The key benefits of DLQI, identified in the guidelines and the literature review, are that:

- It is widely used. A systematic review of the use of QoL instruments in RCTs of patients with psoriasis (n = 100 trials) found that DLQI was the most commonly used quality of life instrument (83 studies, 83%), followed by the SF-36 (31%), EQ-5D (15%), Psoriasis Disability Index (14%) and Skindex (5%).(25)
- It is simple and quick to complete with an average completion time of approximately two minutes. It was deliberately designed for simplicity and ease of interpretation, with the questions fitting onto a single side of A4 paper.
- It has high sensitivity to changes in psoriasis-related endpoints, except in mild disease. (26)
- It is reproducible (high test-retest reliability) and has high internal reliability / internal consistency. (27).
- It has content validity with patients. (28) That is, the questions reflect the reality of the patients' experience of living with psoriasis. (29)
- A specific version has been developed for children, the Children's Dermatology Life Quality Index (CDLQI). It is the most widely used dermatology-specific instrument for measuring quality of life in children. There is evidence of high internal consistency, test–retest reliability, responsiveness to change, and significant correlation with other subjective and objective measures. However, similar to the adult version, Rasch analysis has not been carried out.(30, 31)

The key limitations of DLQI are that:

- The questions focus on physical limitations, and few items address the frequent psychological impact of skin diseases such as low mood and depression.(32) (5)
- It is self-reported and open to interpretation, which may be problematic if relied on for PBS eligibility.
- The DLQI was developed in 1994. When Rasch analysis was subsequently applied, a range of technical issues were identified, notably:
    - Differential item functioning: item responses of many of the questions are affected by external factors such as age and gender, not solely by the level of health related quality of life.(27) Theoretically, this implies that responses to the DLQI by older men and younger women with a similar quality of life impairment cannot be compared.(32)
    - Disordered response thresholds, in particular patients had trouble distinguishing between the response options "a lot" and "very much", (27)
    - Item frequencies showed that large proportions of the samples answered ''not relevant'' to several items. ''Not relevant'' responses are given the same score as the ''not at all'' response. This scoring method presents a problem as individuals who responded ''not relevant'' may actually have had severe illness.(27)

- Inadequate measurement of patients with mild illness. Five of the six subscales have a strong floor effect, suggesting it might have decreased sensitivity to change in mild to severe psoriasis.(33)
- The unidimensionality has been questioned, that is, it calculates a total score from five scales but does not measure a unidimensional construct.(32)

These issues have led some authors to conclude that the DLQI's scientific limitations outweigh the practicalities of its use (32) and recommend that a new measure of functional limitations in dermatology be developed based on modern scaling techniques.(27)

Minimal clinically important difference (MCID) for DLQI

While an MCID of five is commonly cited for the DLQI, this is based on a preliminary study published as an abstract. The most recent, comprehensive study found an MCID of 3.3. From a practical point of view, the authors recommended that an MCID of four should be used in inflammatory skin diseases. This MCID was determined using the anchor-based approach, which incorporates the patient perspective (rather than being based on statistical significance). (26) This is further discussed in Table 17 (Appendix D).

Skindex for assessing quality of life

Given the limitations noted above, other tools for assessing patient impact were also reviewed. The UK NICE 2014 evidence update noted that Skindex, which assesses quality of life, has the potential to address some of the issues with current tools. (10) In particular, Skindex has been shown to have a minimal floor and ceiling effect, and appears to have greater sensitivity to clinical severity than other instruments, particularly in mild psoriasis. Further, a key advantage of Skindex is its greater sensitivity than DLQI in mild psoriasis (which was defined as PASI less than 7). Skindex has a strong correlation with other quality of life instruments including the DLQI. (33)

The UK NICE 2014 evidence update concluded that further validation of Skindex is needed. However, the literature search did not identify any further studies of Skindex that had been published since the UK NICE 2014 evidence update.

The key benefit of Skindex is its greater sensitivity than DLQI in mild psoriasis; *however, this concern may be less relevant to populations with moderate-to-severe psoriasis.*

Note that Skindex was originally developed as a 29 question instrument (Skindex-29), and a reduced version was later developed by applying Rasch analysis (Skindex-17).

Overall

While there are significant limitations with the DLQI, no better instruments appear to be available that are adequately validated. Further, key issues such as the floor and ceiling effect may be less relevant to the PBS subsidy of biologics for which the thresholds for moderate and severe disease are most relevant (rather than distinguishing between different levels of mild disease, or different levels of severe disease).

Correlation between PASI and DLQI

Results of studies of the correlation between PASI and DLQI scores have varied. Overall the correlation between absolute PASI and DLQI scores is not strong (studies have found r2 values between 0.49 and 0.81) but there does seem to be a correlation between an

improvement in PASI and an improvement in the DLQI.(9) (23, 25, 34, 35) Further information is provided in Table 19 (Appendix D).

Development of measures that combine both severity and patient impact

The Simplified Psoriasis Index (SPI) is a three-part multidimensional tool incorporating disease severity, psychosocial impact and historical course.

The first component (disease severity) is derived from the PASI. It involves assessment of the extent of psoriasis in ten body areas. The body sites are weighted to reflect the impact of psoriasis affecting functionally or psychosocially important body sites. Thus, 50% of the total possible extent score is allotted to scalp, face, hands (including nails), feet (including nails), and ano-genital area. A three-point scale is used to record psoriasis involvement in each of the 10 sites. The second component records the patient's assessment of psychosocial impact using a 0–10 visual analogue scale. The third component was designed to reflect the historical ''difficulty'' of disease management by scoring for disease duration and the number of interventions received.

The final score is a three-part summary score (signs, psychosocial disability and interventions). The SPI can be completed by a health-care professional (professional SPI) or the patient (self-assessment SPI)

The UK NICE 2014 evidence update concluded that: "In specialist settings, the SPI appears to be a valid and reliable psoriasis assessment tool that is comparable to other established tools such as the PASI and the DLQI. It appears to provide a simpler and more comprehensive means of psoriasis assessment but further validation in other settings is needed." (10)

However, no additional studies were identified that were published subsequent to the UK NICE 2014 evidence update.

References

1. Baker C, Mack A, Cooper A, Fischer G, Shumack S, Sidhu S, et al. Treatment goals for moderate to severe psoriasis: an Australian consensus.[Erratum appears in Australas J Dermatol. 2014 Feb;55(1):94 Note: Soyer, Peter [corrected to Soyer, H Peter]]. Australasian Journal of Dermatology.54(2):148-54.
2. The Australasian College of Dermatologists. Treatment goals for psoriasis: The Australian Psoriasis Treatment Goals Project https://www.dermcoll.edu.au/wp-content/uploads/ACD-Consensus-Statement-Treatment-goals-for-psoriasis-March-2017.pdf2017
3. Mrowietz U, Kragballe K, Reich K, Spuls P, Griffiths CEM, Nast A, et al. Definition of treatment goals for moderate to severe psoriasis: a European consensus. Archives of Dermatological Research. 2011;303(1):1-10.
4. Smith CH, Anstey AV, Barker JN, Burden AD, Chalmers RJ, Chandler DA, et al. British Association of Dermatologists' guidelines for biologic interventions for psoriasis 2009. Br J Dermatol. 2009;161(5):987-1019.
5. National Institute for Health and Clinical Excellence. Psoriasis: assessment and management. 2012;Clinical Guidance 153.
6. Mrowietz U, de Jong EM, Kragballe K, Langley R, Nast A, Puig L, et al. A consensus report on appropriate treatment optimization and transitioning in the management of moderate-to-severe plaque psoriasis. Journal of the European Academy of Dermatology & Venereology. 2014;28(4):438-53.
7. Armstrong AW, Siegel MP, Bagel J, Boh EE, Buell M, Cooper KD, et al. From the Medical Board of the National Psoriasis Foundation: Treatment targets for plaque psoriasis. Journal of the American Academy of Dermatology. 2017;76(2):290-8.
8. Canadian Psoriasis Guidelines Addendum Committee. 2016 Addendum to the Canadian Guidelines for the Management of Plaque Psoriasis 2009. Journal of Cutaneous Medicine and Surgery. 2016;20(5):375-431.
9. Nast A, Gisondi P, Ormerod AD, Saiag P, Smith C, Spuls PI, et al. European S3-Guidelines on the systemic treatment of psoriasis vulgaris--Update 2015--Short version--EDF in cooperation with EADV and IPC. Journal of the European Academy of Dermatology & Venereology. 2015;29(12):2277-94.
10. National Institute for Health and Care Excellence. Psoriasis, Evidence Update November 2014. A summary of selected new evidence relevant to NICE clinical guideline 153 'The assessment and management of psoriasis' (2012). 2014.
11. American Academy of Dermatology Work G, Menter A, Korman NJ, Elmets CA, Feldman SR, Gelfand JM, et al. Guidelines of care for the management of psoriasis and psoriatic arthritis: section 6. Guidelines of care for the treatment of psoriasis and psoriatic arthritis: case-based presentations and evidence-based conclusions. Journal of the American Academy of Dermatology. 2011;65(1):137-74.
12. National Institute for Health and Care Excellence. Ustekinumab for the treatment of adults with moderate to severe psoriasis (TA180). 2009.
13. National Institute for Health and Care Excellence. Secukinumab for treating moderate to severe plaque psoriasis. 2015.
14. National Institute for Health and Care Excellence. Ixekizumab for treating moderate to severe plaque psoriasis (TA442). 2017.

15. National Institute for Health and Care Excellence. Infliximab for the treatment of adults with psoriasis. 2008.
16. National Institute for Health and Care Excellence. Etanercept and efalizumab for the treatment of adults with psoriasis. 2006.
17. National Institute for Health and Clinical Excellence. Adalimumab for the treatment of adults with psoriasis. 2008.
18. Menter A, Gottlieb A, Feldman SR, Van Voorhees AS, Leonardi CL, Gordon KB, et al. Guidelines of care for the management of psoriasis and psoriatic arthritis: Section 1. Overview of psoriasis and guidelines of care for the treatment of psoriasis with biologics. Journal of the American Academy of Dermatology. 2008;58(5):826-50.
19. Canadian Psoriasis Guidelines Committee. Canadian Guidelines for the Management of Plaque Psoriasis. 2009.
20. Spuls PI, Lecluse LLA, Poulsen M-LNF, Bos JD, Stern RS, Nijsten T. How Good Are Clinical Severity and Outcome Measures for Psoriasis?: Quantitative Evaluation in a Systematic Review. Journal of Investigative Dermatology. 2010;130(4):933-43.
21. Puzenat E, Bronsard V, Prey S, Gourraud PA, Aractingi S, Bagot M, et al. What are the best outcome measures for assessing plaque psoriasis severity? A systematic review of the literature. Journal of the European Academy of Dermatology and Venereology. 2010;24:10-6.
22. Robinson A, Kardos M, Kimball AB. Physician Global Assessment (PGA) and Psoriasis Area and Severity Index (PASI): why do both? A systematic analysis of randomized controlled trials of biologic agents for moderate to severe plaque psoriasis. Journal of the American Academy of Dermatology.66(3):369-75.
23. Heredi E, Rencz F, Balogh O, Gulacsi L, Herszenyi K, Hollo P, et al. Exploring the relationship between EQ-5D, DLQI and PASI, and mapping EQ-5D utilities: a cross-sectional study in psoriasis from Hungary. European Journal of Health Economics.15 Suppl 1:S111-9.
24. Chow C, Simpson MJ, Luger TA, Chubb H, Ellis CN. Comparison of three methods for measuring psoriasis severity in clinical studies (Part 1 of 2): change during therapy in Psoriasis Area and Severity Index, Static Physician's Global Assessment and Lattice System Physician's Global Assessment. Journal of the European Academy of Dermatology & Venereology.29(7):1406-14.
25. Ali FM, Cueva AC, Vyas J, Atwan AA, Salek MS, Finlay AY, et al. A systematic review of the use of quality-of-life instruments in randomized controlled trials for psoriasis. Br J Dermatol. 2017;176(3):577-93.
26. Basra MKA, Salek MS, Camilleri L, Sturkey R, Finlay AY. Determining the Minimal Clinically Important Difference and Responsiveness of the Dermatology Life Quality Index (DLQI): Further Data. Dermatology. 2015;230(1):27-33.
27. Twiss J, Meads DM, Preston EP, Crawford SR, McKenna SP. Can we rely on the Dermatology Life Quality Index as a measure of the impact of psoriasis or atopic dermatitis? Journal of Investigative Dermatology.132(1):76-84.
28. Finlay AY, Basra MK, Piguet V, Salek MS. Dermatology life quality index (DLQI): a paradigm shift to patient-centered outcomes. Journal of Investigative Dermatology.132(10):2464-5.
29. Safikhani S, Sundaram M, Bao Y, Mulani P, Revicki DA. Qualitative assessment of the content validity of the Dermatology Life Quality Index in patients with moderate to severe psoriasis. J Dermatolog Treat.24(1):50-9.

30. Olsen JR, Gallacher J, Finlay AY, Piguet V, Francis NA. Quality of life impact of childhood skin conditions measured using the Children's Dermatology Life Quality Index (CDLQI): a meta-analysis. Br J Dermatol.174(4):853-61.
31. de Jager ME, van de Kerkhof PC, de Jong EM, Seyger MM. A cross-sectional study using the Children's Dermatology Life Quality Index (CDLQI) in childhood psoriasis: negative effect on quality of life and moderate correlation of CDLQI with severity scores. Br J Dermatol.163(5):1099-101.
32. Nijsten T. Dermatology life quality index: time to move forward. Journal of Investigative Dermatology.132(1):11-3.
33. Fernandez-Penas P, Jones-Caballero M, Espallardo O, Garcia-Diez A. Comparison of Skindex-29, Dermatology Life Quality Index, Psoriasis Disability Index and Medical Outcome Study Short Form 36 in patients with mild to severe psoriasis. Br J Dermatol.166(4):884-7.
34. Chaptini C, Quinn S, Marshman G. Durable dermatology life quality index improvements in patients on biologics associated with psoriasis areas and severity index: a longitudinal study. Australasian Journal of Dermatology.57(3):e72-5.
35. Mattei PL, Corey KC, Kimball AB. Psoriasis Area Severity Index (PASI) and the Dermatology Life Quality Index (DLQI): the correlation between disease severity and psychological burden in patients treated with biological therapies. Journal of the European Academy of Dermatology & Venereology.28(3):333-7.
36. Brouwers M KM, Browman GP, Burgers JS, Cluzeau F, Feder G, Fervers B, Graham ID, Grimshaw J, Hanna S, Littlejohns P, Makarski J, Zitzelsberger L for the AGREE Next Steps Consortium. . AGREE II: Advancing guideline development, reporting and evaluation in healthcare. Can Med Assoc J. 2010;182::E839-42.
37. Hsu S, Papp KA, Lebwohl MG, Bagel J, Blauvelt A, Duffin KC, et al. Consensus guidelines for the management of plaque psoriasis. Arch Dermatol. 2012;148(1):95-102.
38. Nast A, Jacobs A, Rosumeck S, Werner RN. Methods Report: European S3-Guidelines on the systemic treatment of psoriasis vulgaris--update 2015--EDF in cooperation with EADV and IPC. Journal of the European Academy of Dermatology & Venereology. 2015;29(12):e1-22.
39. Hamadah IR, Al Raddadi AA, Bahamdan KA, Fatani MI, Alnahdi A, Al Rakban AM, et al. Saudi practical guidelines on biologic treatment of psoriasis. J Dermatolog Treat. 2015;26(3):223-9.
40. Ngan V, Oakely A. Guidelines for the management of psoriasis. 2014.
41. Ohtsuki M, Terui T, Ozawa A, Morita A, Sano S, Takahashi H, et al. Japanese guidance for use of biologics for psoriasis (the 2013 version). Journal of Dermatology.40(9):683-95.
42. Faria JR, Aarao AR, Jimenez LM, Silva OH, Avelleira JC. Inter-rater concordance study of the PASI (Psoriasis Area and Severity Index). Anais Brasileiros de Dermatologia.85(5):625-9.
43. Gourraud PA, Le Gall C, Puzenat E, Aubin F, Ortonne JP, Paul CF. Why statistics matter: limited inter-rater agreement prevents using the psoriasis area and severity index as a unique determinant of therapeutic decision in psoriasis. Journal of Investigative Dermatology. 2012;132(9):2171-5.
44. Singh P, Soyer HP, Wu J, Salmhofer W, Gilmore S. Tele-assessment of Psoriasis Area and Severity Index: a study of the accuracy of digital image capture. Australasian Journal of Dermatology. 2011;52(4):259-63.

45. Otero ME, van Geel MJ, Hendriks JC, van de Kerkhof PC, Seyger MM, de Jong EM. A pilot study on the Psoriasis Area and Severity Index (PASI) for small areas: Presentation and implications of the Low PASI score. J Dermatolog Treat.26(4):314-7.
46. Simpson MJ, Chow C, Morgenstern H, Luger TA, Ellis CN. Comparison of three methods for measuring psoriasis severity in clinical studies (Part 2 of 2): use of quality of life to assess construct validity of the Lattice System Physician's Global Assessment, Psoriasis Area and Severity Index and Static Physician's Global Assessment. Journal of the European Academy of Dermatology & Venereology.29(7):1415-20.
47. Blome C, Beikert FC, Rustenbach SJ, Augustin M. Mapping DLQI on EQ-5D in psoriasis: transformation of skin-specific health-related quality of life into utilities. Archives of Dermatological Research.305(3):197-204.
48. van Geel MJ, Maatkamp M, Oostveen AM, de Jong EM, Finlay AY, van de Kerkhof PC, et al. Comparison of the Dermatology Life Quality Index and the Children's Dermatology Life Quality Index in assessment of quality of life in patients with psoriasis aged 16-17 years. Br J Dermatol.174(1):152-7.

Appendix A – ToR 1 Methods and identification of relevant guidance documents for Q1

Methods

A systematic literature review was performed to identify relevant guidance documents. An OVID Medline search was conducted on 5 June 2017, along with a search of the guidelines databases listed on the AGREE website. A broad strategy was employed using the terms 'psoriasis' or 'guid*' (to capture words such as guidelines and guidance) or 'consensus'. 'Consensus' was included as a search term due to the limited clinical evidence available for some of the issues encompassed by Term of Reference 1, and thus consensus based opinion were useful for specific questions. Table 5 summarises the search and eligibility criteria that were used to address ToR 1, Question 1.

Table 5: Eligibility criteria for literature search for ToR 1 Question 1

Limit	Eligibility criteria
Database searched	OVID Medline
Search terms	1. psoriasis.mp. or exp Psoriasis/ 2. guid*.ti or consensus.ti 3. 1 and 2 4. limit 3 to yr="2007 -Current" The search was conducted on 5 June 2017.

Limit	Eligibility criteria
Other guideline specific databases and websites searched	Per the framework on the AGREE website, the following websites were searched using the term "psoriasis" National Guideline Clearinghouse (www.guideline.gov/) NICE website (www.evidence.nhs.uk/) Canadian Medical Association Infobase: Clinical Practice Guidelines (www.cma.ca/En/Pages/clinical-practice-guidelines.aspx) Scottish Intercollegiate Guidelines Network (www.sign.ac.uk/) National Health and Medical Research Council (www.nhmrc.gov.au/guidelines-publications). eGuidelines (www.guidelines.co.uk/) Guidelines International Network (www.g-i-n.net) Other websites searched using the term "psoriasis": Australian Clinical Practice Guidelines Portal (www.clinicalguidelines.gov.au) DermNet New Zealand (www.dermnetnz.org/)
Publication types	Australian and international evidence-based clinical practice guidelines on the management of CPP involving biologics. English language only
Search period	2007 onwards
Exclusion criteria	Not a clinical practice guideline Not current: not the most up-to-date version of a guideline or more recent guidelines exist for that region Wrong patient population: guidance does not relate to CPP Wrong intervention: does not provide guidance on pharmacological management with biologic drugs (or is specific guidance about only 1 drug) Not in English Healthcare system not similar to Australia

AGREE = Appraisal of Guidelines for Research and Evaluation; CPP = chronic plaque psoriasis; NICE = National Institute for Health and Care Excellence; TOR = term of reference

Endnote was used to automatically remove duplicates. The dataset was then visually scanned and any duplicates not found by Endnote were identified and removed. Articles that met the exclusion criteria, assessed firstly by their title, and secondly by their abstract, were removed.

Potentially relevant guidance documents were assessed using the AGREE II Instrument, which assesses the methodological rigour and transparency in which a guideline is developed. (36) Only guidance assessed as having an overall quality of four or above (on a scale of one to seven) were included in the data extraction.

The PBAC Public Summary Documents for biologics that are PBS-listed for use in CPP were retrieved and reviewed for supplementary information, particular relating to the restriction (including the rationale for the current restriction, requests to change the restriction and information relating to the interpretation of the restriction).

1.3.2 Summary of current clinical guidance

For each of these guidelines, general information such as the primary aim and a brief summary of the method used to develop the guidance was tabulated. Relevant recommendations, evidence statements, consensus statements, general advice and consideration of cost-effectiveness were also tabulated. Where applicable, the strength of the recommendations or the evidence base was summarised. Not all guidelines covered each review question, so only relevant guidance were included in each table.

The PBS restrictions for each of the biologics listed for CPP were summarised. The following information was extracted: clinical criteria for the initial and continuation phases; prior medications; disease severity; the resulting clinical treatment algorithm; timelines for assessment; switching; continuation; and information on special patient populations or circumstances. Relevant comparable data from the guidance documents were also summarised.

1.3.3 Synthesis of findings

Clinical guidance was compared with PBS restrictions. For each review question, the findings have been synthesised into an overall narrative.

Identification of relevant guidelines

The flow chart of the search is presented below. Overall, 181 records were identified (165 through the OVID Medline search and 16 additional records were identified by searching guidelines databases listed on the AGREE website). Of these, 29 published documents were considered relevant, which encompassed 13 separate guidance documents (note that some guidance documents were published in multiple articles e.g. separate chapters for detailed methodology or different topics. Further, the UK NICE technology appraisal guidance for each relevant drug were included).

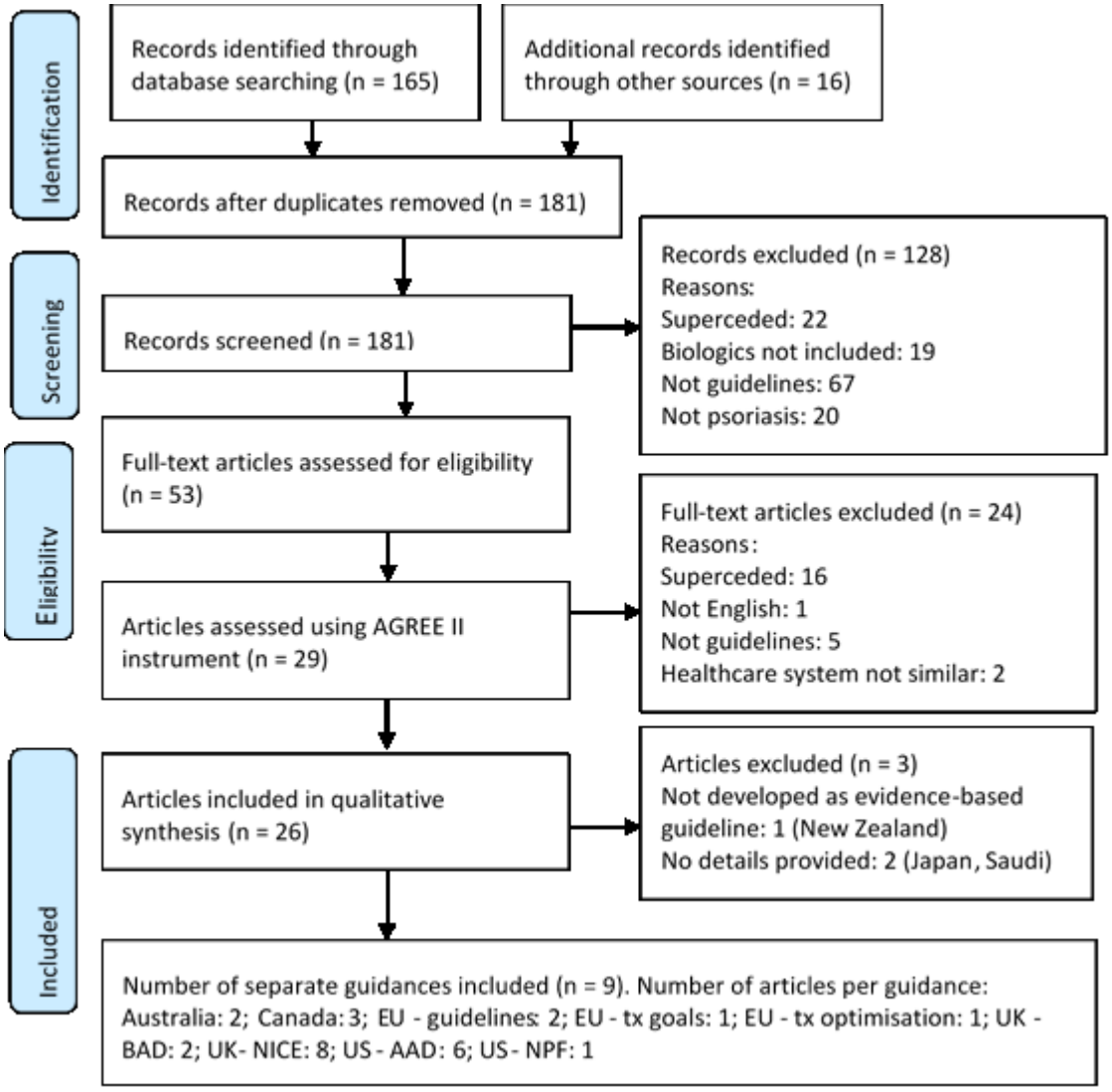


Figure 1: PRISMA Flow Diagram

AAD = American Academy of Dermatology; BAD = British Association of Dermatology; CPP = chronic plaque psoriasis; EU = European Union; NICE = National Institute for Health and Care Excellence; NPF = National Psoriasis Foundation; tx = treatment; UK = United Kingdom; US = United States

The AGREE II appraisals are outlined in the table below.

Table 6: AGREE II assessment of identified guidance documents

	Canada (8, 37)	US NPF (7)	EU (9, 38)	Saudi (39)	UK NICE (5, 10)	NZ (40)	EU tx option (6)	Japan (41)	Australian (1, 2)	US AAD (18)	EU tx goals (3)	UK BAD (4)
Domain 1. Scope and purpose												
1. Objectives	7	7	7	7	7	7	7	7	7	7	7	7
2. Questions	7	7	7	7	7	7	7	7	7	7	7	7
3. Population	7	7	7	7	7	6	7	7	6	7	7	7
Score for domain	100%	100%	100%	100%	100%	94%	100%	100%	94%	100%	100%	100%
Brief rationale: Australian and New Zealand guidelines were stated to cover psoriasis, but only addressed plaque psoriasis.												
Domain 2. Stakeholder involvement												
4. Group membership	6	5	7	1	6	3	5	1	4	5	6	4
5. Target population preferences and views	7	5	6	1	7	1	1	1	3	3	1	5
6. Target users	7	5	7	7	7	3	3	7	3	4	3	7
Score for domain	94%	67%	94%	33%	94%	22%	33%	33%	39%	50%	39%	72%
Brief rationale: US NPF: Specialties of the professionals involved were not identified; patient focus-group discussions were conducted during the pre-Delphi process but it was not clear how these views were incorporated into the guidelines; unclear target audience was. Saudi: No information was available about the development of the guidelines. NZ: no stakeholder involvement. EU tx optimisation consensus: Details of the consensus group were not provided (147 dermatologists who were selected based on their expertise in treating patients with moderate-to-severe psoriasis, only names were provided and unclear how they were selected). Overseen by a steering committee of 9 dermatologists from Europe and Canada (limited details provided). Target users not stated and it was unclear whether this targeted specialists using biologics and/or policy makers. Japan: No information was provided about stakeholder involvement. Australian and US (AAD): Details of each member of the guideline development panel and their role in the group were not provided, target population views were not sought, target users not stated. UK (BAD): Details of each member of the guideline development panel and their role in the group were not provided.												
Domain 3. Rigour of development												
7.Search methods	7	3	7	1	7	1	5	1	3	3	N/A	7
8. Evidence Selection Criteria	5	2	7	1	7	1	3	1	3	3	N/A	7
9. Strengths and limitations of the evidence	6	2	7	2	7	1	6	3	3	5	N/A	7
10. Formulation of recommendations	7	7	7	1	7	1	7	1	4	4	7	7
11. Consideration of benefits and harms	7	N/A	7	5	7	N/A	N/A	5	N/A	7	N/A	7
12. Link between recommendations and evidence	7	2	7	4	7	N/A	6	1	N/A	7	N/A	7

	Canada (8, 37)	US NPF (7)	EU (9, 38)	Saudi (39)	UK NICE (5, 10)	NZ (40)	EU tx option (6)	Japan (41)	Australian (1, 2)	US AAD (18)	EU tx goals (3)	UK BAD (4)
13. External review	7	1	7	3	5	1	N/A	1	1	7	1	7
14. Updating procedure	5	1	7	1	7	1	1	1	1	1	1	3
Score for domain	90%	26%	100%	21%	96%	0%	61%	13%	25%	60%	33%	92%
Brief rationale: Canada: No process was outlined for updating the guidelines. However, a 2016 update was available that used rigorous methodology. US (NPF): Limited details were provided about the literature search and the link between recommendations and supporting evidence. No details provided about the selection of evidence, the strengths/limitations of the evidence, external review or updating processes. Saudi: No information was available about the development of the guidelines including search methods, selection of evidence, formulation of recommendations and updating procedure. Some literature is cited when recommendations are discussed. NZ: Summarises some recently published guidelines (unclear how these were identified). No search strategy was described. No discussion of limitations of each of the guidelines. No external review or updating procedure. No formal recommendations were made (just statements of other guidelines recommendations). EU tx optimisation consensus: scores for questions 7, 8 and 9 are based on those questions that were answered by systematic literature review (not those that were consensus based). Details of the systematic searches were provided and the evidence was graded using the classification of the Oxford Centre for Evidence-Based Medicine levels. The process for formulating recommendations (Delphi panel) was well described. Japan: No information was provided in the English language version about the development of the guidelines. Australia: No details were provided about the literature review. No external review or procedure for updating the guidelines. US (AAD): Limited information about the literature search. Recommendations were developed based on the best available evidence, no other information was provided on the methods for formulating recommendations. No process for updating was reported. UK (BAD): The updating procedure states "a fully revised version is planned for 2012.", but has not been implemented.											
Domain 4. Clarity of presentation												
15. Specific and unambiguous recommendations	7	7	7	3	7	N/A	6	3	7	7	6	7
16. Management options	7	N/A	7	5	7	N/A	N/A	5	N/A	7	N/A	7
17. Identifiable key recommendations	7	6	7	3	6	N/A	5	3	7	7	5	7
Score for domain	100%	92%	100%	44%	94%	N/A	75%	44%	100%	100%	75%	100%
Brief rationale: Saudi: The recommendations are not clear or clearly identifiable. NZ: Summarises other guidelines, rather than making specific endorsed recommendations. Japan: Specific recommendations are provided but some are ambiguous and not clearly presented (e.g. it was unclear whether some were recommendations or discussions of evidence). .												
Domain 5. Applicability												
18. Facilitators and barriers to application	6	5	7	3	7	N/A	3	5	5	5	3	5
19. Implementation advice/tools	5	4	4	2	7	4	2	N/A	4	3	3	5
20. Resource implications	2	1	4	1	6	N/A	1	1	1	2	1	2
21. Monitoring/auditing criteria	6	6	6	6	7	N/A	6	N/A	6	6	6	7

	Canada (8, 37)	US NPF (7)	EU (9, 38)	Saudi (39)	UK NICE (5, 10)	NZ (40)	EU tx option (6)	Japan (41)	Australian (1, 2)	US AAD (18)	EU tx goals (3)	UK BAD (4)
Score for domain	63%	50%	71%	33%	96%	50%	33%	33%	50%	50%	38%	63%
Brief rationale: Resource implications were only considered in NICE UK. All guidelines provided clear criteria on individual patient treatment goals, however only UK NICE and BAD provided population treatment goals. Canada, US NPF, Japan, Australia, US AAD and UK BAD: Discussed some facilitators/barriers particularly regarding health system and roles of various health professionals and limitations in implementing, but these were not comprehensively discussed. EU tx optimisation consensus: Limited tools and resources were available to facilitate application. Acknowledged that access barriers and resource implications were not taken into account in formulating the recommendations. EU tx goals consensus: Limited tools and resources were available to facilitate application, as European guidelines are intended to be adapted to national or regional circumstances. Saudi: Limited information was provided about facilitators/barriers. No implementation tools were provided. Japan: Implementation advice/tools were deemed not applicable because these may be available in Japanese (which would be more relevant). Australian: Stated the next step will be to educate dermatologists and GPs, but did not state how this education would occur. US AAD: No tools/resources were provided to facilitate application. UK BAD: Some checklists and tools are available on the BAD website.											
Domain 6. Editorial independence												
22. Funding body	7	1	7	1	7	3	2	1	1	7	5	3
23. Competing interests	7	5	7	7	7	3	3	5	4	7	5	7
Score for domain	100%	33%	100%	50%	100%	33%	25%	33%	25%	100%	67%	67%
Brief rationale: US NPF: Funding provided by the National Psoriasis Foundation, which also participated in the interpretation of data and review and approval of the manuscript. US NPF, Japan: Conflicts of interest of authors are stated, but no information is provided about how these were addressed. Saudi, Australia: The funding source was not stated and there was no explicit statement whether the funding body influenced the final recommendations. DermNet NZ: Organisation is funded by various sources including non-directed sponsorship. No explicit statements about the role of funding sources or the conflicts of interest of the authors have been provided. UK BAD: Guidelines are produced and funded by the British Association of Dermatologists (website states it is funded by the activities of its members). EU tx optimisation consensus: Funded by Abbott through an educational grant, which included funding to a medical communications agency, payment of consultancy fees to members of the steering committee. It was stated that Abbott had no influence on the development of the manuscript nor did it review the content of the manuscript. EU tx goals consensus: Supported by an unrestricted grant from Abbott. The article stated that the sponsor had no influence on the programme and financial transactions were processed through the finance department of the grant designee.											
Total	89%	54%	94%	41%	96%	31%	55%	37%	50%	71%	56%	84%
Overall quality (1 to 7)	7	4	7	3	7	2	4	3	4	5	4	6
I would recommend this guideline for use	Yes	Yes with modifications	Yes	No	Yes	No	Yes with modifications	No	Yes with modifications	Yes	Yes with modifications	Yes
Overall notes US NPF, EU tx options, EU treatment goals, Australian: Intended as consensus documents to address specific questions. Saudi: No details were provided about guideline development, the literature search, the funding source. NZ: Summarises other guidelines, rather than an independent guideline. Japan: The English language version was assessed which did not provide any details regarding methodology. Australian: Limited details about the literature search, the panel, conflicts of interest, funding source and target audience. UK BAD: High quality guideline. Published in 2009, and the website states that there is an update in progress (as at 20 June 2016).												

AAD = American Academy Dermatology; AGREE = Appraisal of Guidelines for Research and Evaluation; CPP = chronic plaque psoriasis; NICE = National Institute for Health and Care Excellence; TOR = term of reference BAD = British Association of Dermatologists; EU = European Union; NPF = National Psoriasis Foundation; NZ = New Zealand; opt = optimisation; UK = United Kingdom; US = United States; tx = treatment

The table below summarises the overall assessment of the quality of the guidance documents.

Table 7: Summary of AGREE II quality appraisal

Guidance	Comments	Included
Australian, ACD 2017(2)	Baker 2013 (below) was adapted for use by health professionals by the ACD. The resulting consensus statement was approved by the ACD Board of Directors.	Yes (combined with Baker 2013, below)
US NPF, 2017 (7)	Intended as consensus document regarding treatment targets for plaque psoriasis, rather than as comprehensive guidelines.	Yes due to its relevance and recentness
Canada, 2016 update (8, 37)	High quality, with detailed and rigorous: methodology; consultation processes; selection of evidence; processes for developing recommendations and high levels of editorial independence.	Yes
EU, 2015 (9, 38)	High quality, with detailed and rigorous: methodology; consultation processes; selection of evidence; processes for developing recommendations and high levels of editorial independence.	Yes
Saudi, 2015 (39)	Insufficient details about the guideline development process, methodology, the literature search and the funding sources.	No, assessed as having overall quality of 3 (on a scale of 1 to 7).
UK NICE, 2014 update (5, 10)	High quality, with detailed and rigorous: methodology; consultation processes; selection of evidence; processes for developing recommendations and high levels of editorial independence.	Yes
EU tx optimisation consensus, 2014 (6)	Intended as a consensus on treatment optimisation and transitioning, rather than a guideline. When assessed as a formal guideline it was of marginal quality. Where possible, systematic literature reviews were conducted. If this was not possible a modified Delphi procedure was used consisting of several stages: a round of question prioritisation; then draft answers were sent to national faculties to be discussed during national meetings; then revised answers were discussed at an international meeting where formal voting on the level of agreement with draft answers was conducted. The process involved 147 dermatologists and was funded by Abbott.	Yes, as it was the underlying basis for other guidance documents and addressed questions no other guidance document covered .
NZ, 2014 (40)	Aimed to summarise other guidelines, rather than as an independent evidence-based guideline, developed through a formal guideline development process (e.g. no consensus by experts).	No assessed as having overall quality of 3 (on a scale of 1 to 7).
Japan, 2013 (41)	Insufficient details about the guideline development process, methodology, the literature search and the funding sources. This information may have been available in the Japanese language version, but was not in the English version.	No assessed as having overall quality of 3 (on a scale of 1 to 7).
Australian, Baker 2013 (1)	Intended as a consensus of treatment targets for CPP, rather than a guideline. It was based on an EU consensus statement (Mrowietz et al, 2011) and aimed to develop Australian treatment goals, taking into account the local medical environment and differences in prescribing patterns. When assessed as a formal guideline it was of marginal quality, due to the lack of details/methods regarding stakeholder involvement, rigour of development, unclear target audience and unclear funding source.	Yes, due to its relevance to the target question
US AAD, 2011 (18)	Reasonable quality, but lacked details regarding the methods for stakeholder involvement, rigour of development (details of search strategy and evidence selection criteria).	Yes

Guidance	Comments	Included
EU tx goals consensus, 2011 (3)	Intended as a consensus of treatment targets for CPP, rather than a guideline. When assessed as a formal guideline it was of marginal quality (e.g. no literature search). Two formal consensus methods were used: a consensus conference and the Delphi technique.	Yes, as it was the underlying basis for many other guidance documents.
UK BAD 2009 (4)	High quality. Included, but it is noted that this was published in 2009 using similar methodology to the UK NICE guidance, and the website states it is in the process of being updated	Yes

AAD = American Academy of Dermatology; ACD = Australasian College of Dermatologists; BAD = British Association of Dermatology; CPP = chronic plaque psoriasis; EU = European Union; NICE = National Institute for Health and Care Excellence; NPF = National Psoriasis Foundation; NZ = New Zealand; tx = treatment; UK = United Kingdom; US = United States

Guidance documents were included in the data extraction if they were assessed as having an overall quality of four or higher (on a scale of one to seven) or were of particular relevance to the ToR. Five documents were included despite not being comprehensive, evidence-based guidelines. These were two Australian, a US (National Psoriasis Foundation) and two EU consensus statements (3) (6). Four of these related to treatment targets for plaque psoriasis. They were included given their relevance to the target question. The other was an EU consensus on treatment optimisation and transitioning. It addressed questions that were not covered by any other guidance (i.e. topics for which there was a lack of reliable evidence and so were addressed via a consensus process involved 147 dermatologists).

The consensus statements included two that were Australian:

- Baker 2013, which was developed through a consensus panel comprising 12 dermatologists.(1) It was based on a European consensus statement on treatment targets,(3) which the panel adapted to take account of the Australian medical environment and differences in prescribing patterns.
- Australasian College of Dermatologists (ACD) 2017, which was based on Baker 2013 and "adapted for use by health professionals" by the ACD.(2)

The two documents are referred to in this review as the "Australian consensus". The only difference between the two related to terminology about CPP severity, which did not affect the treatment targets or algorithm. Both included two categories of disease severity with the same thresholds and treatment recommendations: Baker 2013 termed the two categories 'mild' and 'moderate-to-severe' CPP; while ACD 2017 termed them 'mild-to-moderate' and 'severe' CPP.

Documents that were excluded based on the quality assessment (using the AGREE II tool) were the New Zealand, Japanese and Saudi documents. The New Zealand document aimed to summarise other guidelines. The Japanese and Saudi documents lacked details or rigorous methodology about the development process, the literature search and the funding sources.

The UK British Association of Dermatology (BAD) guidance was included, however it was published in 2009 and the website states it is in the process of being updated (as at 22 August 2017).

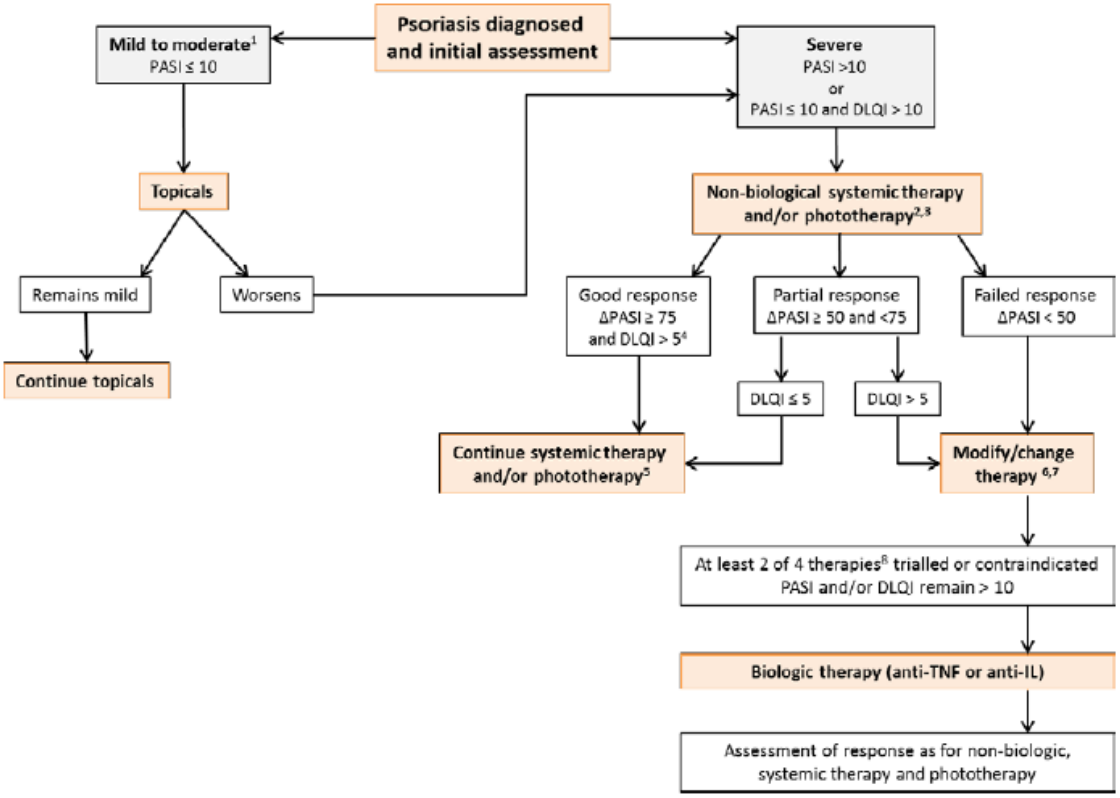
The EU guidelines had a narrower scope than other evidence based guidelines and focused on systemic treatments. Treatment goals (i.e thresholds to initiate biologics and stay on biologics) were not specifically addressed, but rather re-iterated from the EU treatment goals consensus. Other guidelines from EU countries (which were deemed to have been superseded by the EU guidelines: Swiss and German) also re-iterated this consensus statement.

Importantly, none of the guidelines comprehensively addressed resource implications. The only guidelines to partially consider resource implications were the UK NICE guidelines, which considered cost effectiveness in making recommendations, but not the overall resource implications of implementing the guidelines.

Appendix B - ToR 1 Q1 Additional Results tables

Table 8: Treatment algorithms proposed in relevant guidance documents

	PBS restrictions	Guidelines			Consensus
		Canada (8)	EU (9)	UK NICE (10)	Australian (1, 2)
1st line for mild disease	-	Routine skin care and/or topical therapy. Focus on HRQoL.		Traditional topical therapies (e.g. corticosteroids, vitamin D and vitamin D analogues, dithranol and tar preparations). Use for up to 4 weeks as initial treatment for adults with trunk or limb psoriasis.	Topical therapies
2nd line	Phototherapy: UVB or PUVA 3 times per week for ≥ 6 weeks; Methotrexate: ≥ 10mg weekly for ≥ 6 weeks; Cyclosporin: ≥ 2mg/kg per day for ≥6 weeks; Acitretin: ≥ 0.4mg/kg per day for ≥ 6 weeks	No clinical reason to reserve the biologics for 2nd line use. To ameliorate moderate to severe plaque psoriasis: use acitretin (limited evidence in monotherapy), cyclosporin (short term), or methotrexate. To achieve complete control use biologicals or phototherapy.	Phototherapy, methotrexate, cyclosporin (recommended if a short course for induction treatment is intended. It should be used for a maximum of up to 2 years, especially short term) and fumaric acid esters. (Could not make a recommendation for or against the use of acitretin as a monotherapy based on the available evidence).	Phototherapy (UVB) if not controlled by topical therapies. Systemic non-biologicals (methotrexate, cyclosporin and acitretin) if: -not controlled with topical therapy; AND -significant impact on physical, psychological or social wellbeing; AND -≥1 of: PASI > 10; OR psoriasis is localised with significant functional impairment and/or high levels of distress; OR phototherapy is ineffective, cannot be used or has resulted in rapid relapse.	Phototherapy, methotrexate, cyclosporin and acitretin.



Notes

1. In absence of modifying features such as visible site, genital, palmoplantar, nails involvement, pruritus with excoriation (see definition on Page 3).
2. Appropriate time to review varies with each treatment and the range is 6 – 24 weeks.
3. Non-biologic therapies include methotrexate, cyclosporin and acitretin.
4. Psoriasis area severity index (ΔPASI) ≥75 but dermatological quality of life index (DLQI) ≥5 may occur if modifying features such as the visible site, genital, palmoplantar, nail involvement or pruritus are present or the response is discordant with patient's expectations. Physician assessment whether to continue, modify or change therapy.
5. Continuation/discontinuation is modulated by toxicity and contraindication.
6. Treatment change to take into account patient wishes.
7. In addition to change of treatment, modify may include adding topicals, adding other systemic treatment, increasing dose or frequency or hospital admission.
8. The Australian consensus group propose that two of four therapies as reasonable and best practice. The current requirement of the Australian reimbursement body, the Pharmaceutical Benefits Scheme, is three of four therapies.

Figure 2: Treatment goals algorithm proposed by the Australian consensus (2)

Source: Figure on page 5 of Australasian College of Dermatologists 2017
DLQI = Dermatology Life Quality Index; IL = interleukin; PASI = Psoriasis Area and Severity Index; TNF = tumor necrosis factor
Note: The only difference compared with the algorithm proposed in Baker 2013 was that "Mild to moderate" was termed "mild", and "Severe" was termed "Moderate/severe" (PASI and DLQI thresholds were unchanged).

Table 9: Severity assessment of psoriasis

	Guidelines			Relevant consensus	
	Canada [a] (8)	EU (9)	US AAD (18)	Australian [b] (1, 2)	EU tx goals (3)
Mild	Disease with a minimal impact on QoL; acceptable level of symptomatic control with routine skin care measures and/or topical therapy.	Referred to EU tx goals consensus.	<5% of BSA and usually not involving the face, genitals, hands or feet;	PASI ≤ 10 and DLQI ≤ 10	BSA ≤ 10 and PASI ≤ 10 and DLQI ≤ 10.
Moderate	Not controlled by routine skin care measures and/or Significantly affects QoL, due to the extent, the physical discomfort or location (e.g., the face, hands, feet, or genitals).	Referred to EU tx goals consensus.	≥5% BSA; or concurrent PsA; or in vulnerable area eg. face, genitals, hands or feet, scalp; or causing major QoL issues.		Moderate-to-severe: PASI > 10 or BSA > 10; <u>and</u> DLQI > 10[d] Mild disease may be classified as moderate-to-severe if involvement of: visible areas, scalp, genitals, palms, soles, onycholysis or onychodystrophy of ≥2 fingernails, itch leading to scratching, or recalcitrant plaque/s.
Severe	Disease that cannot be, or would not be expected to be, satisfactorily controlled by topical therapy and that causes severe degradation of the patient's QoL.			PASI > 10 <u>and/or</u> DLQI > 10 Per EU tx goals except only 1 of either PASI or DLQI is required to be > 10; and also included pruritus leading to excoriation (rather than scratching) and deleted "presence of single recalcitrant plaque".	

	Guidelines			Relevant consensus	
	Canada [a] (8)	EU (9)	US AAD (18)	Australian [b] (1, 2)	EU tx goals (3)
Outcome measures	Numerical cut-offs are poorly suited to routine clinical practice because they fail to reflect patients' actual burden of disease.	Used both the PASI and DLQI to integrate both the dermatologist's and the patient's judgement.	Noted that QoL measures are important for clinical decision making. Noted PASI not commonly used in clinical practice & is less sensitive if <10% BSA involvement		

BSA = body surface area; CPP = chronic plaque psoriasis; DLQI = Dermatology Life Quality Index; EU = European Union; PASI = Psoriasis Area and Severity Index; PsA = psoriatic arthritis; QoL = quality of life; tx = treatment

[a] Stated in text, not an official recommendation.

[b] The two categories were referred to as "mild" and "moderate-to-severe" in Baker 2013.

Table 10: Continuation and discontinuation criteria for biologics in CPP

	PBS restrictions	Guidelines [a]			Relevant consensus statements			
		Canada (8)	UK NICE (5)	UK BAD	US NPF (7)	Australian (1)	EU tx optimisation (6)	EU tx goals (3)
When to assess patient for initial response	After ≥ 12 wks of tx. Initial tx comprises up to: Adalimumab etanercept, ixekizumab & secukinumab = 16 wks; infliximab = 22 wks; ustekin = 28 wks.		Assess at 12 to 16 weeks, depending on drug: Adalimumab = 16 wks; etanercept = 12 wks; infliximab = 10 wks; ixekizumab = 12 wks; sekukinumab = 12 wks ustekinumab = 16 wks	Refers to NICE and product license. Adalimumab = 16 wks; etanercept = 12 wks; Infliximab = 10-14 wks, ustekinumab = 16-28 wks	3 months (out of choices of 3, 4 or 6 months).	Assess at end of induction phase. Induction phase = 16 to 24 wks (for longer onset of action)		Induction: until week 19, however can be extended to week 24 (depending on drug and dose).
To continue with the same regimen	ΔPASI ≥ 75% versus baseline	Clinical endpoints of treatment success should rely on pt satisfaction, HRQoL and traditional objective indicators of disease response.[b]	Adequate response: ΔPASI ≥ 75% versus baseline; OR ΔPASI 50% and DLQI ≤5 from when treatment started.	Same as UK NICE	At 3 months post-initiation: - <u>acceptable</u> response (adequate or sufficient) either BSA ≤3% or ΔBSA ≥ 75% versus baseline. - <u>target</u> response BSA ≤1%. During maintenance (every 6 months) target response is BSA ≤1%.	Good response: ΔPASI ≥75 and DLQI ≤ 5 Partial response: ΔPASI 74-50% and DLQI ≤ 5 (continue regimen.) Other: ΔPASI ≥75 and DLQI ≥5: physician decision [c]	Stated that there is no established definition of inadequate clinical response. Noted that in RCTs a primary non-response was defined as not achieving PASI 50.	Treatment success: ΔPASI ≥75 Intermediate response: ΔPASI 74-50% and DLQI ≤ 5 (continue regimen.)

	PBS restrictions	Guidelines [a]			Relevant consensus statements			
		Canada (8)	UK NICE (5)	UK BAD	US NPF (7)	Australian (1)	EU tx optimisation (6)	EU tx goals (3)
Strength of recommendation	-	Expert Opinion (Level of Evidence: 4; Grade D)	From Technology appraisal guidance (RCT + expert opinion).	Not a formal recommendation (discussed in text).	Consensus	Consensus	Consensus	Consensus
To continue (face, palm of hand, sole of foot)	A reduction in all three PASI subscores to 'slight' or 'none' or ≥75% reduction in the area affected	-				Considered the PBS definitions were appropriate & could be combined with the proposed DLQI assessment.		
If adequate response not achieved	Discontinue if ΔPASI < 75%. If inadequate response to 3 biologics, cease PBS-subsidised therapy for 5 yrs.[d]		Discontinue individual drug if adequate response not achieved following initiation period, or if it is not maintained. If inadequate response to a 2nd biological drug, seek supra-specialist advice.		Treatment targets are in the context of individualized evaluation of benefit-risk assessment and elicitation of patient preferences. They are not to be used to deny access to therapies.	Per EU consensus on treatment goals	1.Increase dose for adalimumab, etanercept and ustekinumab. Reduce dosing interval for infliximab. Consider combining with conventional tx. 2.If above have been considered, switch to another drug.	Modify regimen: Treatment failure: If ΔPASI ≥50% not achieved. Intermediate response: If ΔPASI 74-50% and DLQI >5. Modification strategies: adjust dose; add another tx (combination tx); switch tx.

BAD = British Association of Dermatology; BSA = body surface area; CPP = chronic plaque psoriasis; DLQI = Dermatology Life Quality Index; EU = European Union; HRQoL = health related quality of life; LoE = level of evidence; NICE = National Institute for Health and Care Excellence; NPF = National Psoriasis Foundation; PASI = Psoriasis Area and Severity Index; PBS = Pharmaceutical Benefits Scheme; pts = patients; RCT = randomised, controlled trials; tx = treatment; UK = United Kingdom; US = United States; wks = weeks

[a] The EU guidelines did not make any recommendations, but the two EU consensus statements were referred to in the discussion, citing the PASI and DLQI thresholds from the EU consensus on treatment goals, and the regimen modification strategies if an adequate response is not achieved from EU consensus on treatment optimisation. Further, the US (AAD) guidelines are not included in above table because no guidance was provided regarding therapy continuation. However the US (AAD) guidelines outline some options for modifying treatment. It noted that loss of efficacy over time may occur with all of the TNF-alfa antagonists. At this point, the choices include: increasing the dosage (seldom approved by third-party payers); combination therapy; or switching to another agent.

[b] As a "Key Point": For some pts, amelioration may be an adequate treatment goal. However, full clearance represents an appropriate goal in treating many pts.

[c] Per EU consensus on treatment goals, but also noted ΔPASI ≥75 but DLQI ≥ 5 may occur e.g. if the psoriasis is on a visible site, genital, palmoplantar, nail involvement or pruritus or response is discordant with patient's expectations. In these case, the consensus recommended physician assessment whether to continue, modify or change therapy.

[d] Patients who fail to respond to tx with 3 biologics are deemed to have completed this treatment cycle and must cease PBS-subsidised therapy. These pts may recommence a new biological treatment cycle after a minimum of 5 years has elapsed.

[e] The EU consensus: tx optimisation outlined strategies for primary and secondary non-responders. For adalimumab, increase dose (LoE 3); For etanercept: increase dose (LoE 4); For ustekinumab: increase the dose and if not successful reduce dosing interval (LoE 2); for infliximab, reduce dosing interval (LoE 4). Alternatively, combination strategies with conventional treatments can be considered. (LoE 5). If above have been considered, switch to another drug (consensus).

Table 11: Guidance's for use of biologics in special populations and circumstances

PBS	Canada (8)	US AAD (11)	UK BAD (4)
Children			
Etanercept is the only PBS-listed biologic for CPP in pts aged <18 yrs. Eligibility includes (for whole body [a]): -failed ≥ 2 of 3 txs (phototherapy, MTX, acitretin); and - PASI > 15. Max. 24 weeks per course. Re-treatment if pt experiences exacerbation or fails to respond. Re-treatment due to disease flare if: PASI > 15 or ΔPASI ≥ 50%. If fail to respond twice, ≥ 12 month break.	Etanercept is the best-studied biologic for paediatric psoriasis. Ustekinumab and adalimumab are being evaluated. Noted a 2010 systematic review that recommended etanercept as third-line (calcipotriol ± topical steroids first line; methotrexate as systemic treatment of choice).	Limited data on the use of biologics for psoriasis in in pts aged <18 yrs. One study of etanercept in this age group: 57% of pts aged 4 - 17 years achieved PASI-75 versus 11% in placebo group. Etanercept dose was 0.8 mg/kg once weekly. Algorithm for pts <18yrs with >5% BSA (without PsA): First line: topical agents. Second line if UVB available: phototherapy ± methotrexate. If UVB not available: adalimumab, etanercept, infliximab, cyclosporin, MTX, PUVA. (Notes etanercept has level 1 evidence to support this recommendation).	Etanercept recommended for severe psoriasis in pts ≥8 years who fulfil criteria (Strength of recommendation A; LoE 1++). Etanercept therapy should be initiated at dose of 0.8mg/kg weekly (Strength of recommendation A; LoE 1++). In patients who respond, treatment may be continued according to clinical need, although long-term data on efficacy are limited to 1 year (Strength of recommendation A; LoE 1+)
Infection risk			
			-Monitor pts on biologics for early signs and symptoms of infection throughout treatment (Strength of recommendation C; LoE 2+) - Warn pts about risk factors for Salmonella and Listeria (Strength of recommendation D; LoE 4)

PBS	Canada (8)	US AAD (11)	UK BAD (4)
Vaccination			
-	All psoriasis treatments except acitretin may affect the outcome of vaccination. For pts receiving biologics: - inactivated or subunit-based vaccines are generally thought to be safe and effective. - use of live or live-attenuated vaccines is not recommended due to the theoretical risk that it could produce an infection.	Pre-commencement of biologic tx Standard vaccinations, including pneumococcal, hepatitis A and B, influenza, and tetanus-diphtheria are recommended. Vaccination while receiving biologics: Biologic therapies may potentially impair the immune response to vaccinations. Most studies in pts treated with TNF blockers show adequate but attenuated immune responses to pneumococcal or influenza vaccination. Once immunosuppressive therapy has begun, avoid vaccination with live vaccines (including varicella; mumps, measles, and rubella; oral typhoid; yellow fever) and live-attenuated vaccines (including intranasal influenza and the herpes zoster vaccine). Physicians should consider the advantages and disadvantages of administering killed virus vaccines such as influenza.	• Update patients vaccines before starting biologics (Strength of recommendation D LoE 4) • Patients should not receive live or live attenuated vaccinations < 2 weeks before, during, and for 6 months after discontinuing biologics (Strength of recommendation D; LoE 4) • Inactivated vaccines are safe to administer concurrently with biologics (Strength of recommendation B; LoE 2++) • Where possible, inactivated vaccines should be administered 2 weeks before starting therapy to ensure optimal immune responses (Strength of recommendation D LoE 4) • TNF blockers may lead to reduced antibody responses to influenza vaccine. TNF blockers in combination with methotrexate may lead to reduced antibody responses to pneumococcal vaccine (Strength of recommendation B; LoE 2++) • Patients should receive pneumococcal and influenza vaccines while on biologic therapy (Strength of recommendation D; LoE 4)
Elective surgery			
	Withhold TNF blockers for ≥1 week before and after surgery (as may increase risk of post-surgical infection). Acknowledges that the optimal period is not known and some studies suggest pre-operative discontinuation may not be required.		• TNF blockers should be discontinued at least four half-lives prior to major surgery (2-12 wks depending on drug). (Strength of recommendation D; LoE 4) • Biologic therapy can be restarted postoperatively if there is no evidence of infection and wound healing is satisfactory (Strength of recommendation D; LoE 3)

PBS	Canada (8)	US AAD (11)	UK BAD (4)
TB			
	Noted the TNF blockers are associated with serious infections such as reactivated TB.	Reactivation of TB has been associated with TNF blockers. Pts on TNF blockers are at higher risk for developing TB.	• Assess pts for active and latent TB before starting biologics, especially if high risk (Strength of recommendation B; LoE: 2+) • Pts with active or latent TB should receive treatment prior to initiating biologic therapy (Strength of recommendation B; LoE 2+)
Hepatitis B or C			
	TNF blockers may be safe with appropriate screening and monitoring. Hep B: Screen for HBV before initiating treatment with a TNF blocker. In HBV-positive patients with inactive disease, a course of antiviral therapy is recommended, starting 2–4 weeks before the TNF blocker. Then close follow-up while on biologic to monitor liver function and viral load. Isolated instances of hepatitis B reactivation and hepatic complications have been observed in patients on TNF blockers.	Hep C: Exercise caution if using TNF blockers in pts with Hep C infection. Consultation with liver specialist may be appropriate, and monitoring of serum aminotransferases and viral load are recommended. Hep B: TNF-a promotes viral clearance: Screen pts before treatment. Notes there is an FDA warning suggesting that patients with HBV should not be treated with any of the TNF blockers.	• There is insufficient evidence to recommend biologics in patients with known chronic, potentially harmful, viral infections and clinicians should seek specialist advice on a case-by-case basis (Strength of recommendation D; LoE 4) • In patients who are Hep C carriers, there is limited evidence to support the use of etanercept if evaluated and monitored during therapy (Strength of recommendation D, LoE 4) • TNF antagonist therapy should be avoided in chronic carriers of Hep B due to risk of reactivation (Strength of recommendation D; LoE 4).

PBS	Canada (8)	US AAD (11)	UK BAD (4)
Pregnancy			
	Notes the Medical Board of the National Psoriasis Foundation: Use TNF blockers (or cyclosporin) "with caution" as a third-line option. Biologics may be considered when the benefits clearly outweigh the risks. Notes that biologics are FDA classification "B" based on no malformations seen with etanercept or infliximab, and few animal studies available. The guidelines note there are no specific contraception guidelines on the need for contraception in patients taking biologics.	Relatively minimal data on the use of the biologics during pregnancy. Noted adalimumab, etanercept and infliximab are pregnancy category B. Noted that infliximab and etanercept have been rarely associated with the VACTERL syndrome (vertebral, anal, cardiovascular, tracheoesophageal, renal, and limb abnormalities) when used during pregnancy. Careful consideration of the risks and benefits of TNF blockers is warranted before they are used to treat psoriasis in pregnant women.	• Pregnancy should be avoided in patients with psoriasis receiving biologic therapy. (Strength of recommendation D; LoE 3) • If planning a pregnancy, biologics should be avoided during the first 12 weeks (Strength of recommendation D; LoE 3) • If patients on biologics discover they are pregnant, refer to specialist fetal medicine unit. Consideration should be given to stopping biologic (Strength of recommendation D; LoE 4) • Notwithstanding the above, patients should be assessed on a case-by-case basis and the risks to the mother of stopping the biologic should be balanced against any potential harm (Strength of recommendation D; LoE 4) • For patients receiving infliximab during pregnancy, infusions should be avoided after 30 weeks if at all possible due to long half-life and evidence it crosses the placenta and may persist for several months in the fetal circulation (Strength of recommendation D; LoE 3) • Breast feeding should be avoided in patients receiving biologics although limited evidence indicates that infliximab is not excreted in breast milk (Strength of recommendation D; LoE 4)

BSA = body surface area; FDA = Food and Drug Administration; HBV = hepatitis B virus; Hep = hepatitis; LoE = level of evidence; MTX = methotrexate; PsA = psoriatic arthritis; PUVA = psoralen plus ultraviolet A;TB = tuberculosis; TNF = tumour necrosis factor; UV = ultraviolet. Note: TNF blockers are adalimumab, etanercept, and infliximab. Note that secukinumab and ustekinumab, which are not TNF-alfa blockers, were not available at the time of initial development of these guidelines (though ustekinumab was available in the Canadian 2016 update).

[a] For psoriasis affecting the face, palm of hand and sole of foot. PBS-eligibility includes that the pt must have failed / be intolerant to/ be contraindicated to ≥ 2 of 3 txs (phototherapy, MTX, acitretin). The criteria indicating failure to achieve an adequate response to prior treatment include: ≥2 of 3 PASI subscores for erythema, thickness and scaling are rated as severe or very severe; or the skin area affected is ≥ 30% or more of the face, palm of a hand or sole of a foot.

Patients are eligible for re-treatment due to disease flare if: (i) all subscores are rated moderate to severe, or 2 of the three subscores are rated severe to very severe; OR (ii) the area affected is ≥ 30% of the face, palm of a hand or sole of a foot, or the skin area affected is a ≥50% or greater change compared to the most recent response assessment following cessation of the most recent 24 weeks of PBS-subsidised etanercept.

Appendix C – ToR 1 Methods Q2

The clinical assessment measures recommended or discussed in the guidance documents (identified in Question 1) were summarised. PASI and DLQI were the most commonly recommended clinical assessment measures used to evaluate the severity of CPP or stages for disease progression.

A literature review was performed to identify articles about these two measures. A focused strategy was employed using the terms 'DLQI', 'Dermatology Life Quality Index', 'PASI' or 'Psoriasis Area and Severity Index' in the title to identify only articles specifically about the outcome measure. Table 12 summarises the search and eligibility criteria that were used to address Question 2 of Term of Reference 1.

Table 12: Eligibility criteria applied to the search for articles about DLQI and PASI

Limit	Eligibility criteria
Database searched	OVID Medline
Search terms	Two searches were conducted. 1. For articles about DLQI 1. psoriasis.mp. or exp Psoriasis/ 2. (DLQI or Dermatology Life Quality Index).ti. 3. 1 and 2 4. limit 3 to yr="2010 -Current" 1. For articles about PASI 1. psoriasis.mp. or exp Psoriasis/ 2. (PASI or Psoriasis Area and Severity Index).ti. 3. 1 and 2 4. limit 3 to yr="2010 -Current" The searches were conducted on 28 June 2017.
Publication types	English language only
Search period	2010 onwards
Exclusion criteria	Not about the outcome measure Not about plaque psoriasis

DLQI = Dermatology Life Quality Index; PASI = Psoriasis Area and Severity Index

In addition, pertinent references from the guidelines were retrieved.

Two highly targeted searches were conducted for Skindex (Skindex-17 and Skindex-29) and the Simplified Psoriasis Index. These were conducted because the UK NICE 2014 practice update noted key advantages of these measures, but considered further validation would be required before either could be recommended.

Table 13: Eligibility criteria for the search for articles about Skindex

Limit	Eligibility criteria
Database searched	OVID Medline
Search terms	1. psoriasis.mp. or exp Psoriasis/ 2. skindex.mp 3. 1 and 2 4. limit 3 to yr="2014 -Current" The search were conducted on 30 June 2017.
Publication types	English language only
Search period	2014 onwards (i.e. the period after the UK NICE 2014 evidence update)
Exclusion criteria	Not about the outcome measure (e.g. were reporting results from a clinical trial) Not relevant to psoriasis Not about Skindex

NICE = National Institute for Health and Care Excellence; UK = United Kingdom

Table 14: Eligibility criteria for the search for articles about Simplified Psoriasis Index

Limit	Eligibility criteria
Database searched	OVID Medline
Search terms	Simplified Psoriasis Index.mp.
Search period	2014 onwards (i.e. the period after the UK NICE 2014 evidence update)
Exclusion criteria	Already included in UK NICE 2014 evidence update Review article (no new clinical evidence)

NICE = National Institute for Health and Care Excellence; UK = United Kingdom

Summary of outcomes

Clinical assessment measures discussed or recommended in the guidance documents (identified in Question 1), along with the rationale for selection of particular measures, were tabulated and summarised. Recommendations were distinguished from general discussion.

Relevant articles from the literature search were reviewed and summarised. In particular, the key benefits and limitations of the PASI, DLQI, Skindex and SPI were noted, along with comparisons against other outcome measures. Further, the correlation between the DLQI and PASI was assessed.

Synthesis of findings

The findings have been synthesised into an overall narrative.

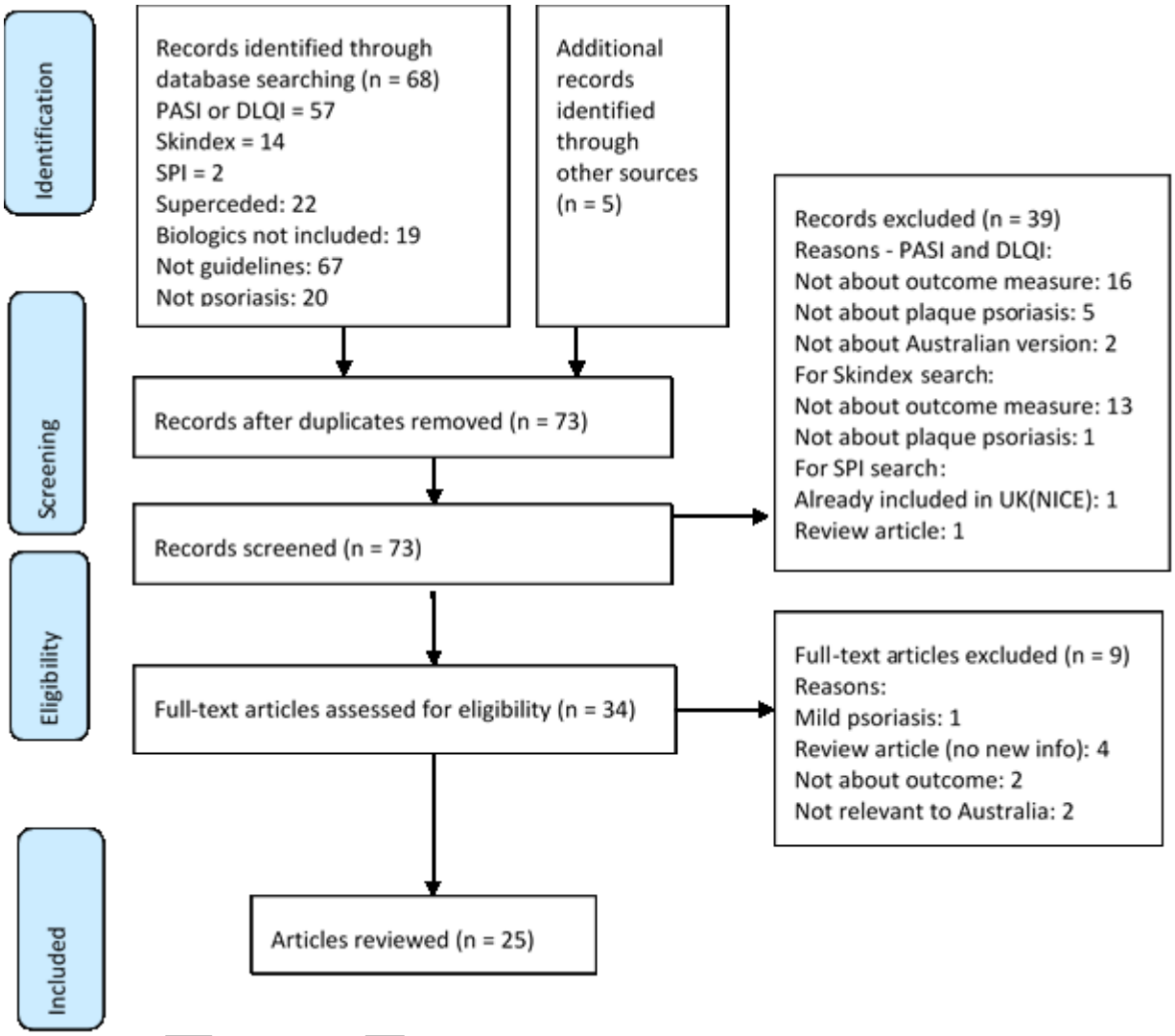


Figure 3: Results of the literature review, PRISMA Flow Diagram

DLQI = Dermatology Life Quality Index; PASI = Psoriasis Area and Severity Index; SPI = Simplified Psoriasis Index UK = United Kingdom

Appendix D– ToR 1 Results Q2

Table 15: Outcome measures recommended in guidance's and rationale

Discussion of outcome
Evidence based guidelines
Canada (8)
Recommendations: HRQoL factors should be central to the long-term management of psoriasis (Level of Evidence 4) GRADE D. Metrics such as the PDI, DLQI, DQOLS, SF-36, or the PSA Scale should be used when practical, particularly in patients with self-reported dissatisfaction in treatment response despite improvement in clinical parameters of disease activity (Level of Evidence 4) GRADE D. Discussion The guidelines noted that there are no large-scale RCTs to evaluate the comparative utility of the different scales during routine clinical visits or the optimal frequency of assessment.
EU (9)
Recommendations: The guidelines recommend objective assessment of the disease (such as PASI, BSA, PGA) and assessment of HRQoL (such as DLQI, Skindex-29 or -17) as pre-treatment and during treatment for all systemic therapies. Discussion Acknowledged that none of these measures capture the seriousness of the long term condition. Noted that PASI 75 can be achieved in the majority of patients with the therapies currently available. With the availability of new biologic agents namely the anti-IL-17A, anti-IL-17RA, and anti-IL-23p19 antibodies treatment efficacy can be increased in a high number of patients. For such therapies a PASI 90 response may be discussed as a new treatment goal in the future. The Introduction of the guidelines refer to (and provide the treatment algorithm from) the EU treatment goals consensus which states that for defining treatment goals it was consented to use PASI and DLQI in order to integrate both the dermatologist's and the patient's judgement. Noted that: PASI was used in all the trials and was the most commonly used tool for assessing psoriasis severity; DLQI is the most commonly used score for assessing the impact of psoriasis on HRQoL. Although there is no correlation between absolute PASI and absolute DLQI scores, there seems to be a correlation between an improvement in PASI and an improvement in the DLQI.
UK NICE (5, 10)
Recommendations In specialist settings, a validated tool should be used to assess severity (e.g. PASI). In specialist settings, and if practical in non-specialist settings, use a validated tool to assess the impact on physical, psychological and social wellbeing, e.g. DLQI (or CDLQI for younger people). In any healthcare setting, record: PGA; the patient's assessment of current disease severity, for example, using the static Patient's Global Assessment; the BSA; any involvement of nails, high-impact and difficult-to-treat sites.

Discussion of outcome
Discussion In arriving at these recommendations, NICE comprehensively assessed the validity and reliability of tools for measuring psoriasis. The outcomes considered were: • Construct validity: limited data suggested that the CoPSI and LS-PGA demonstrated good correlation with PASI. One systematic review showed that the outcomes of PASI 75 and 0 or 1 on PGA are highly correlated in people with moderate to severe psoriasis treated with biologics. For HRQoL, PDI was the most convergent with DLQI. • Internal consistency: Inter-rater/observer reliability: variable results for PASI, with the correlation ranging from 0.73-0.91. Fewer studies for other tools but the LS-PGA and CoPSI may also have adequate inter-rater reliability, with static and dynamic PGA consistently being reported as less reliable. •Intra-rater or test-retest reliability: PASI and pt-assessed BSA performed well. More limited evidence suggested that LS-PGA and CoPSI may also have good re-test reliability. Static and dynamic PGA appeared to have lower intra-rater reliability. Limited evidence for this outcome for QoL measures: SPI performed better than DLQI. •Practicability: None of the tools have been evaluated in primary care, but use would be justified when practical and possible (introduction would take time and training). •Sensitivity to change: The Guideline Development Group noted that PASI is considered insensitive at the lower end of the disease severity spectrum. In milder disease a PGA of clear or nearly clear is a reasonable correlate with PASI. PGA is not useful in more severe disease (PASI was considered the gold standard). No evidence was found for the use of the tools in children, in primary care settings or for different psoriasis phenotypes. The Guideline Development Group agreed that guideline recommendations should align with the existing NICE Technology Appraisals for biologics. The methods document notes that PASI and DLQI are routinely used in clinical practice as they are part of the eligibility criteria for biologics for funding approval. Overall, the PASI was chosen for use in specialist settings: this tool performed at least at an adequate level for the prioritised outcomes (intra-rater reliability, inter-rater reliability and sensitivity to change); healthcare professionals in specialist settings are already trained in its use and interpretation; the majority of clinical trials use PASI and therefore treatment effects are quantified using this tool; although the PASI has limitations, there are no other validated tools that are clearly superior at present. The Guideline Development Group chose the DLQI to assess impact of all types of psoriasis because this is a simple, practical tool that performed at least adequately in the prioritised outcomes (i.e. the outcomes outlined above), and in the absence of high quality evidence to indicate other tools were better. However, the limitations of the DLQI were acknowledged as significant including inadequate capture of the psychological impact of psoriasis, including on mood, and that it does not capture wellbeing or coping. The Skindex-17 may have advantages in this regard but at present there is very limited evidence of its validity and reliability in people with psoriasis. Other notes When using PASI: take into account skin colour and make appropriate clinical adjustments (erythema may be underestimated in people with darker skin types, such as skin types V and VI on the Fitzpatrick scale).

Discussion of outcome
When using the DLQI: take into account any physical, sensory or learning disabilities, or communication difficulties, that could affect the responses to the DLQI and make appropriate adjustments. When using an assessment tool: take account of patient age, any disabilities or language / communication difficulties. Provide help and support if needed to ensure that the chosen assessment tool continues to be a sufficiently accurate measure.
US AAD (18)
Recommendations No specific measures were recommended. Discussion Noted PASI is commonly used in trials, but the authors considered it to be less sensitive in patients with lower BSA involvement (<10%). Also stated that PASI was rarely used in clinical practice (in the US). Stated that measures such as PGA and target plaque scores, together with % BSA involvement are commonly used assessment tools, particularly for milder disease. In clinical practice, the physician generally uses subjective qualitative assessment of the severity of a patient's psoriasis by combining objective assessment of the BSA involvement, disease location, thickness, and symptoms, presence or absence of psoriatic arthritis with the subjective assessment of the physical, financial, and emotional impact of the disease on the patient's life.
UK BAD (4)
Recommendations PASI and DLQI Discussion Noted that all existing disease severity assessment tools are imperfect and most require some training. PASI was chosen as it has been widely used in clinical trials and had also been adopted by NICE. Noted that the DLQI is a validated tool for the measurement of HRQoL across all skin diseases, including psoriasis, and has been used in both trial and clinical practice settings. A score of > 10 has been shown to correlate with at least 'a very large effect' on an individual's quality of life. When using the PASI and DLQI to determine whether or not a patient should be considered for biologic therapy, clinicians should take into account the applicability of these measures to each individual patient. There are circumstances where the use of these tools fails to give a sufficiently accurate assessment of the clinical situation. With respect to the PASI, this is especially pertinent in patients with localized disease that involves special 'high-impact' sites (genitalia, hands, feet, head and neck) where highly significant functional and ⁄or psychosocial morbidity may exist with a PASI < 10. The DLQI may be a poor indicator of emotional disabilities resulting from psoriasis and the validity of the DLQI (and of other quality of life measures) may also be undermined due to linguistic or other communication difficulties
Consensus statements
US NPF (7)
The consensus expressed a preference for a single criterion to determine treatment success (rather than using multiple assessment tools). Advantages of single criterion: ease of use in clinical practice and less administrative burden. Noted that the disadvantage is that the criterion may not encompass other important aspects of the disease burden. The most preferred instrument was BSA, but it was acknowledged that this does not encompass HRQoL (patients perspective was that BSA does not capture location, symptoms, comorbidities, or life quality).

Discussion of outcome
Australian (1, 2)
DLQI should be taken into account as patients progress through systemic, including biologic, therapy in Australia. Noted that the PBS does not take into account DLQI in determining treatment success or failure, while other countries do (e.g. UK, Scotland, Spain and Germany). There was unanimous agreement to use DLQI as the measure of impact on HRQoL because it is: (i) supported by strong evidence; (ii) the most commonly used worldwide; and (iii) valid and easy to use. Considered that DLQI would identify a group who might otherwise be considered to have mild disease, while also giving some indication of patient satisfaction with treatment. Noted BSA was included by EU consensus on treatment goals. Omitted because it is not routinely used in Australian clinical practice and adds little clinical value to the PASI score.
EU consensus on tx goals (3)
BSA and PASI were chosen for the grading of psoriasis symptoms and extent of lesions. PASI was chosen because it is: commonly used in clinical practice and trials; and has been shown to be a reliable instrument to evaluate treatment success or failure when patients are scored at baseline before treatment initiation and while on therapy. Acknowledged that PASI has some methodological limitations, however based on clinical considerations and the later generation of treatment goals, it was decided to use the established scores. The article noted that a major drawback of the PGA is the lack of a common definition thus it was not included (despite being widely used). It was further decided to include an instrument to assess HRQoL in order to employ an independent measure of patient-reported psoriasis severity. DLQI was selected for HRQoL because it was most widely used, available in all languages represented by the consensus group, accessible on the internet and has a reliable grading system. The article also noted it has been used worldwide in numerous clinical trials and investigations on life quality and burden of disease. There is a definition of the different scores of the DLQI and their impact on patients' life which allows a reliable grading of HRQoL. By using this definition, a DLQI < 5 indicates only mild impact on an individual patients' quality of life. The article noted there were country-specific differences in the preferred instrument, with Skindex-29 and SF-36 used in some countries as a primary tool to measure HRQoL.

AAD = American Academy of Dermatology; BAD = British Association of Dermatology; BSA = body surface area; CDLQI = Children's Dermatology Life Quality Index; CoPSI = Copenhagen Psoriasis Severity Index; DLQI = Dermatology Life Quality Index; DQOLS = Dermatology Quality-of-Life Scales; EU = European Union; HRQoL = Health-Related Quality of Life; IL = interleukin; LS-PGA = Lattice System Physician's Global Assessment; NICE = National Institute for Health and Care Excellence; NPF = National Psoriasis Foundation; PASI = Psoriasis Area and Severity Index; PBS = Pharmaceutical Benefits Scheme; PDI = Psoriasis Disability Index; PGA = Physician's Global Assessment; PSA Scale = Psoriatic Arthritis Scale; RCT = randomised controlled trial; SF-36 = Short Form Health Survey; UK = United Kingdom; US = United States

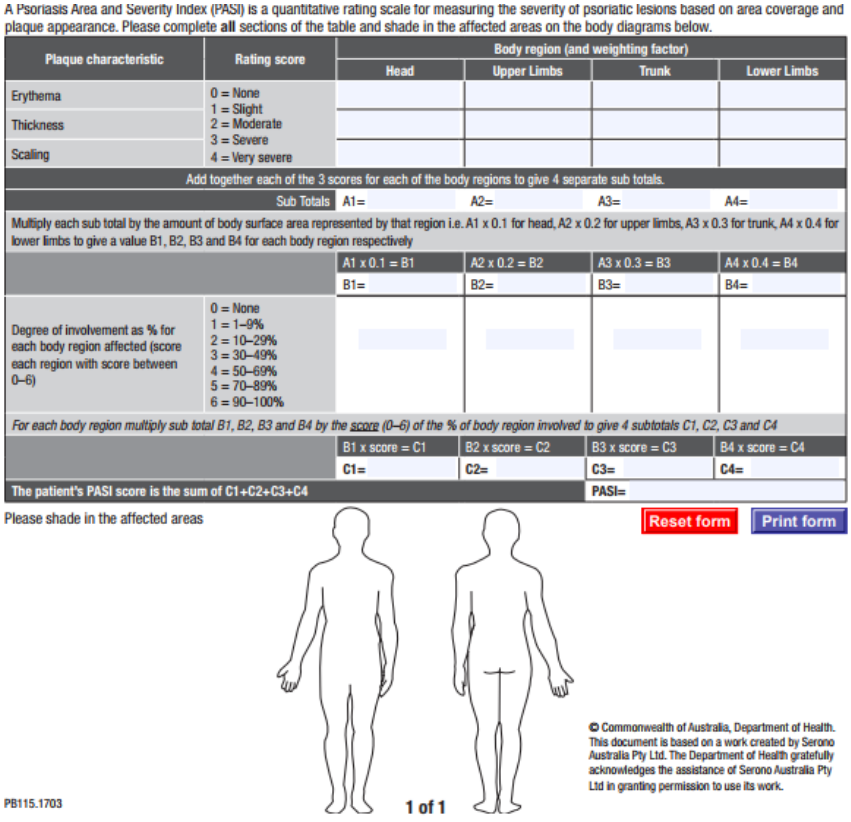
Table 16: About the PASI

PASI
Strengths • Most commonly used psoriasis assessment tool in Australia. It is also the most commonly used outcome in clinical trials. • Most extensively validated score (i.e. has the most number of studies conducted about its overall validity) (20) (21) *thus its limitations are known.* • Generally high intra-rater reliability (test-retest reliability) and moderate to high inter-rater reliability if measured in specialist settings. (20) *While some studies found higher variation, this may have been affected by the experience level of the evaluator.(20) Overall, the studies assessing inter-rater and intra-rater reliability were generally of poor quality with limited information about methodology e.g. Faria 2010 did not state whether the assessors were blinded to the ratings given by the other assessors.(42)* Gourraud 2012 argued that due to the asymmetric distribution of the PASI, commonly used statistics should not be used to assess inter-rater reliability (they argued the validity of the PASI is overrated because of the contribution of the high scores reached by the rare but most severe patients). In simulated examples, Gourraud 2012 found that when restricting the analysis to patients with a PASI <20, inter-rater agreement severely decreased (r = 0.38, p = 0.41).(43) *However, overall review articles have concluded that the PASI has high intra-rater reliability and moderate to high inter-rater reliability.(5, 20, 21)* • Could potentially be measured by telehealth. Singh 2011 compared PASI scores assessed by dermatologists at face-to-face consults versus PASI scoring based on digital images (two dermatologists assessed each patient in each setting, 12 patients were recruited). Comparison between the face-to-face and tele-scores revealed good (κ = 0.67 and 0.63) agreement for the scorers respectively.(44) Limitations • Does not incorporate the patient perspective. It also does not incorporate pain, itch and pigmentation which may all impact on patient quality of life. • Complex and resource intensive. • Lacks sensitivity to disease that affects a small body area (10) (e.g. hands, nails, feet, face, and genitals) and it is also not adapted for flexural and scalp locations of psoriasis. A minimal involvement (<10% BSA) will always lead to an area of 1. (45) • Not validated in children or very young children (see section on children) • There is no consensus on interpretation of the clinical meaning of changes in PASI. Further, it is non-linear which makes it difficult to interpret. It lacks sensitivity at the lower end of its range and the upper half of its range is redundant. (21) (20) • To meet regulatory requirements, a severity measure that provides a word-based result (e.g. severe, mild, almost-clear, etc.) is desired. • The 3 features (erythema, scale, induration) are co-dependent.(10) • Spuls 2010 considered that PASI had moderate content validity because plaque elevation was not given a higher weight, as the authors considered that plaque elevation was the most significant clinical sign of psoriasis. • The BSA must be determined separately for each segment of the body, which may induce errors, particularly if there are small degrees of involvement. Reviews of the overall validity of PASI and other measures of psoriasis severity Two comprehensive reviews (Puzenat 2010 and Spuls 2010) evaluated the quality of the measures used to assess psoriasis severity, including analysing each

PASI
measure for its construct validity, content validity, internal consistency, intra-observer variation, sensitivity to change, and acceptability/time required to perform measurement.(20, 21) The reviews found that PASI had: • low construct validity (ability to measure the disease, extent to which the scores correlate with other outcome measures) notably because it did not capture HRQoL. • Content validity (whether the items of the score are representative the disease). While one review used it as the gold standard against which to assess other measures, the other review ranked the content validity as moderate because plaque elevation was not given more weight. • High intra-rater reliability (test-retest) and moderate to high inter-rater reliability. Overall, both reviews found that none of the scoring tools met all of the validation criteria, however: • Puzenat 2010 considered that PASI was the most extensively studied and most thoroughly validated. Ultimately, the study recommended the PASI for both scientific and clinical scoring of psoriasis severity.(21) • Spuls 2010 looked at additional measures such as responsiveness, response distribution and interpretability. The PASI scored poorly on each of these measures (see 'limitations'). Overall, they noted that PASI is the most commonly used clinical measure in research, but that it has substantial limitations such as low response distribution, no consensus on interpretability and low responsiveness in mild disease. LS-PGA scored the most highly across the validity measures, followed by PGA. Overall, no best instrument was identified, and different situations may call for different measures. (20) Overall, Spuls 2010 concluded "When choosing a measure, it is important to determine the most needed features, for example, good responsiveness or sensitivity in mild disease. It may be necessary to combine two or more scores to satisfy all needs. For example, PASI may not be particularly sensitive for mild disease, but it may be outstanding for a study in which patients have severe disease. It also provides the advantage of a large base of studies in which it has been used. Another instrument may have some characteristics that are better, but this may not outweigh the benefit of being able to compare with the existing database of studies that used PASI. For interventional studies responsiveness is important, which points to some newer measures like the PLASI and PEASI. In cross-sectional studies interpretability is important which favors the PGA, SAPASI, and LS-PGA. If someone would do a mail survey of psoriasis patients, the SAPASI is preferred because this measure is developed for patient assessment. If future authors want a reliable instrument, then the LS-PGA and PASI would be best, with the PGA a close follow-up". (20) <u>Correlation of PASI with other measures (PGA, LS-PGA and sPGA)</u> In light of the limitations of PASI, several other measures have been developed that assess psoriasis disease severity, notably: **PGA:** PGA involves an average assessment of all psoriatic lesions based on erythema, scale, and induration. It does not quantify BSA or evaluate individual lesion locations. It is straightforward and easy to understand (thus NICE considered it to be suitable for use in primary care). Multiple versions exist, many of which lack clear definitions. This was considered to be a major drawback by the EU treatment goals consensus group, who did not recommend this tool. (3) Further, the range of definitions makes it difficult to compare results across different trials. **LS-PGA:** The LS-PGA is similar to the PGA, but takes a quantitative approach to the global assessment of disease severity by integrating ranges of involved BSA and the overall plaque morphology. As such, it combines the % BSA affected (7-point scale) and average of plaque qualities of thickness, erythema and scale (4 point scale). The two scores are combined in a lattice to give an overall rating from clear to very severe. Compared with PASI, the LS-PGA gives more weight to induration compared with scaling and erythema. Its validity and reliability have been shown to be very good. Psoriasis severity is stratified in eight categories

PASI
(clear to very severe) and most of the scale was used (high responsiveness and interpretability compared with the PASI).(5, 20, 21) However, it is used far less frequently in clinical trials (no RCTs were identified that used it as a primary outcome), and only 3 studies were identified that assessed the validity of LS-PGA, versus 28 for PASI. (20) **sPGA:** The static PGA is a 5, 6, 7 or 8-point rating ranging from "clear" to "very severe" psoriasis. It evaluates the global severity without respect of baseline characteristics. In addition, 5 to 8-point scales are used and there is no consensus on scale definition.(21) Studies have generally found a high correlation between PASI and PGA, LS-PGA and sPGA, leading some authors to conclude the tools are substantially redundant and one alone is sufficient: • Robinson 2011 conducted a systematic review of RCTs that measured both PASI and PGA in patients with moderate-to-severe CPP. They compared the % of patients achieving both PASI 75 and PGA 0 or 1 (clear or almost clear) at 3 time periods: 8 to 16 weeks; 17 to 24 weeks; and greater than 24 weeks. They found that PASI and PGA correlate very closely except at the lower bounds of therapeutic efficacy. The r^2 values for the correlation between PASI 75 and PGA 0 or 1 were 0.92 at 8 to 16 weeks and 0.89 at 17 to 24 weeks. The authors concluded that the 2 tools are substantially redundant and either alone is a sufficient tool for assessing psoriasis severity in patients with moderate to severe CPP. Because the PASI is better validated and more detailed, it remains the score of choice for clinical trials, but the simpler PGA may be well suited for community-based outcomes projects.(22) *The authors did not discuss quality-assessment of the included studies.* • Heredi 2014 also found a high correlation (r^2 = 0.92, p<0.05) between PASI and PGA VAS.(23) • Chow 2015 compared PASI, sPGA, and LS-PGA in a trial of systemic treatments for CPP. Patients were randomized to voclosporin or cyclosporin for 24 weeks (the '24-week-treatment' group, n = 366), or placebo for 12 weeks followed by voclosporin for 12 weeks (the 'initial-placebo' group, n = 89). All scoring systems changed in parallel and were sensitive enough to detect reductions in severity during placebo therapy as well as with active therapy (P < 0.01 for each measurement). At study onset, there were poorer correlations between sPGA and PASI (r = 0.45) and LS-PGA (r = 0.39); than between PASI and LS-PGA (r = 0.68). After therapy, all correlations were stronger, but sPGA continued to be less well correlated (with PASI, r = 0.85; with LS-PGA, r = 0.79) than LS-PGA with PASI (r = 0.90). Two- or three-step improvements in LS-PGA showed very good to excellent accuracy in corresponding to PASI 50 and PASI 75, respectively, and were more accurate than comparable changes in sPGA. The authors concluded that the 3 measures correlate well overall.(24) In Part 2 of this study, Simpson 2015 measured the correlation of the 3 scores with the DLQI, to assess construct validity. The study found that all 3 severity measures (PASI, sPGA, and LS-PGA) were moderately and positively correlated with DQLI, indicating construct validity. (46)

BSA = body surface area; CPP = chronic plaque psoriasis; LS-PGA = Lattice System Physician's Global Assessment; NICE = National Institute for Health and Care Excellence; PASI = Psoriasis Area and Severity Index; PGA = Physician's Global Assessment; RCT = randomised controlled trial; sPGA = static Physician's Global Assessment; SAPASI = self-administered PASI



A Psoriasis Area and Severity Index (PASI) is a quantitative rating scale for measuring the severity of psoriatic lesions based on area coverage and plaque appearance. Please complete **all** sections of the table and shade in the affected areas on the body diagrams below.

Plaque characteristic	Rating score	Body region (and weighting factor)			
		Head	Upper Limbs	Trunk	Lower Limbs
Erythema	0 = None 1 = Slight 2 = Moderate 3 = Severe 4 = Very severe				
Thickness					
Scaling					
Add together each of the 3 scores for each of the body regions to give 4 separate sub totals.					
Sub Totals		A1=	A2=	A3=	A4=
Multiply each sub total by the amount of body surface area represented by that region i.e. A1 x 0.1 for head, A2 x 0.2 for upper limbs, A3 x 0.3 for trunk, A4 x 0.4 for lower limbs to give a value B1, B2, B3 and B4 for each body region respectively					
		A1 x 0.1 = B1	A2 x 0.2 = B2	A3 x 0.3 = B3	A4 x 0.4 = B4
		B1=	B2=	B3=	B4=
Degree of involvement as % for each body region affected (score each region with score between 0–6)	0 = None 1 = 1–9% 2 = 10–29% 3 = 30–49% 4 = 50–69% 5 = 70–89% 6 = 90–100%				
For each body region multiply sub total B1, B2, B3 and B4 by the score (0–6) of the % of body region involved to give 4 subtotals C1, C2, C3 and C4					
		B1 x score = C1	B2 x score = C2	B3 x score = C3	B4 x score = C4
		C1=	C2=	C3=	C4=
The patient's PASI score is the sum of C1+C2+C3+C4				PASI=	

Please shade in the affected areas

Reset form Print form

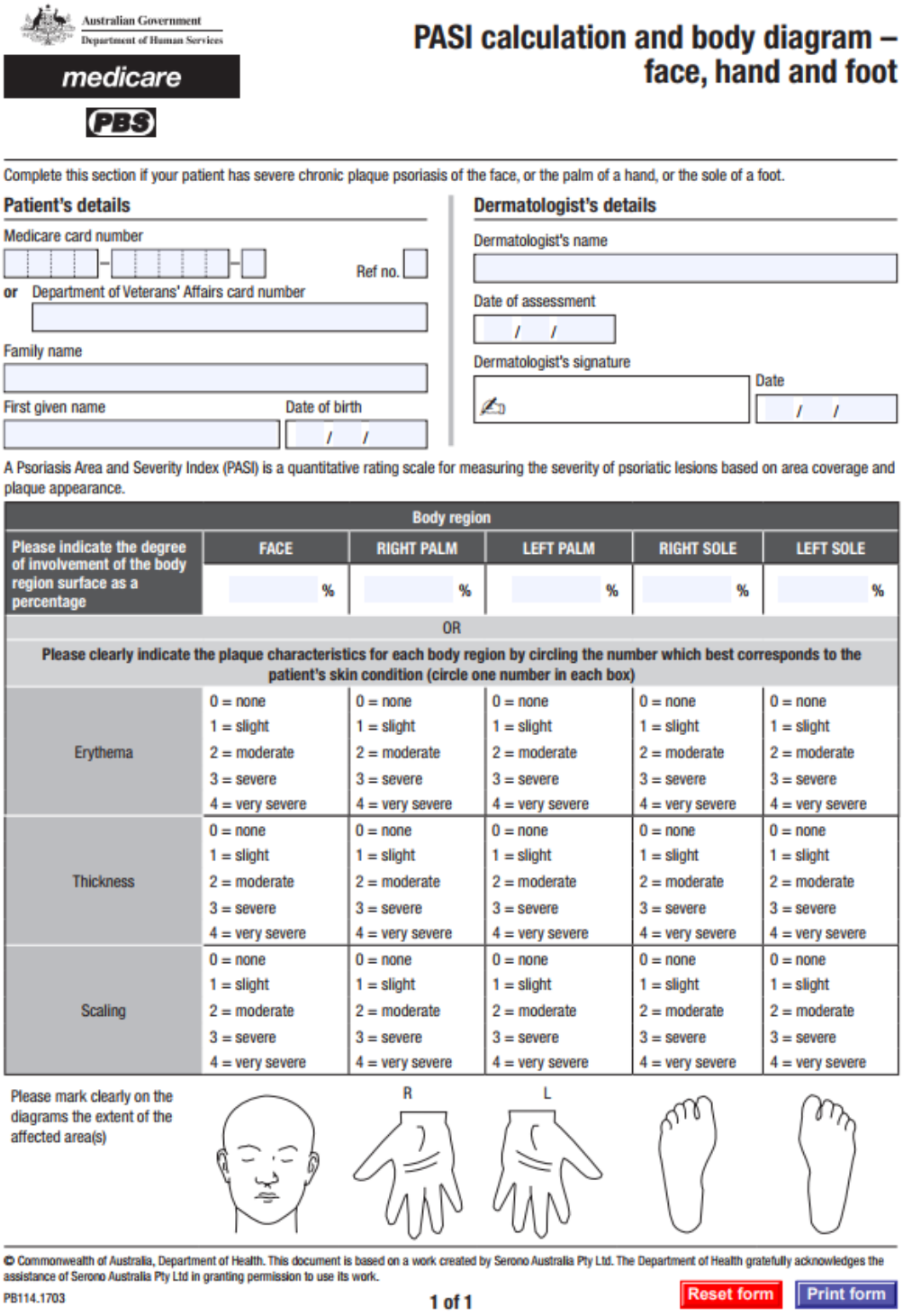
PB115.1703

1 of 1

Figure 4: Measurement of PASI (whole body)

Source: https://www.humanservices.gov.au/health-professionals/forms/pb115 (Accessed 3 July 2017)

PASI = Psoriasis Area and Severity Index



Australian Government
Department of Human Services

medicare

PBS

PASI calculation and body diagram – face, hand and foot

Complete this section if your patient has severe chronic plaque psoriasis of the face, or the palm of a hand, or the sole of a foot.

Patient's details

Medicare card number

Ref no.

or Department of Veterans' Affairs card number

Family name

First given name

Date of birth / /

Dermatologist's details

Dermatologist's name

Date of assessment / /

Dermatologist's signature

Date / /

A Psoriasis Area and Severity Index (PASI) is a quantitative rating scale for measuring the severity of psoriatic lesions based on area coverage and plaque appearance.

	Body region				
Please indicate the degree of involvement of the body region surface as a percentage	**FACE**	**RIGHT PALM**	**LEFT PALM**	**RIGHT SOLE**	**LEFT SOLE**
	%	%	%	%	%
OR					
Please clearly indicate the plaque characteristics for each body region by circling the number which best corresponds to the patient's skin condition (circle one number in each box)					
Erythema	0 = none 1 = slight 2 = moderate 3 = severe 4 = very severe	0 = none 1 = slight 2 = moderate 3 = severe 4 = very severe	0 = none 1 = slight 2 = moderate 3 = severe 4 = very severe	0 = none 1 = slight 2 = moderate 3 = severe 4 = very severe	0 = none 1 = slight 2 = moderate 3 = severe 4 = very severe
Thickness	0 = none 1 = slight 2 = moderate 3 = severe 4 = very severe	0 = none 1 = slight 2 = moderate 3 = severe 4 = very severe	0 = none 1 = slight 2 = moderate 3 = severe 4 = very severe	0 = none 1 = slight 2 = moderate 3 = severe 4 = very severe	0 = none 1 = slight 2 = moderate 3 = severe 4 = very severe
Scaling	0 = none 1 = slight 2 = moderate 3 = severe 4 = very severe	0 = none 1 = slight 2 = moderate 3 = severe 4 = very severe	0 = none 1 = slight 2 = moderate 3 = severe 4 = very severe	0 = none 1 = slight 2 = moderate 3 = severe 4 = very severe	0 = none 1 = slight 2 = moderate 3 = severe 4 = very severe

Please mark clearly on the diagrams the extent of the affected area(s)

R L

Reset form Print form

Figure 5: PASI calculation and body diagram - face, hand and foot

Source: https://www.humanservices.gov.au/health-professionals/forms/pb114 (Accessed 3 July 2017)

PASI = Psoriasis Area and Severity Index

Table 17: About the DLQI

DLQI
Strengths ● Widely used. A systematic review of the use of QoL instruments in RCTs of patients with psoriasis (n = 100 trials) found that DLQI was the most commonly used QoL instrument (83 studies, 83%), followed by the SF-36 (31%), EQ-5D (15%), Psoriasis Disability Index (14%) and Skindex (5%).(25) ● Simple and quick to complete with an average completion time of approximately 2 minutes. It was deliberately designed for simplicity and ease of interpretation. ● High responsiveness/sensitivity to changes in psoriasis-related endpoints, except in mild disease. (26) ● High internal reliability / internal consistency. (27) ● Reproducible (has high test-retest reliability). (27) ● High face validity / content validity with patients. (28) That is, the questions accurately reflect patients' experiences of living with psoriasis. This was also demonstrated in a study by Safikhani 2013 who conducted interviews with 21 patients with moderate-to-severe psoriasis. Patients were first asked open-ended questions about the impact of psoriasis on their lives and activities. The DLQI was then administered and cognitive debriefing interviews assessed patients' understanding of the instructions, items, response scales and relevance of the specific items to their experience with psoriasis. Patients' responses to open-ended questions were consistent with DLQI concepts and generally did not provide additional concepts. Most participants reported that the instructions, item content and response scales were clear and easy to understand and relevant.(29) ● There is a published algorithm to convert DLQI to EQ-5D, however it has significant limitations in validity and clinical relevance. (47) ● Well correlated with the societal costs of psoriasis. ● Available in 90 languages. ● Only 1 version. (28) Limitations ● Questions focus on physical limitations, and few items address the psychological impact.(32) The UK NICE guidelines noted that DLQI may not be sensitive enough to an important aspect of wellbeing: low mood and depression.(5) ● Self-reported. ● Not disease-specific (covers a range of dermatological conditions). ● Technical issues including: - differential item functioning: item responses of more than half of the questions are affected by external factors such as age and gender, not solely by the level of HRQoL. Theoretically, this implies that responses to the DLQI by older men and younger women with a similar HRQoL impairment cannot be compared.(32) - disordered response thresholds, e.g. patients had trouble distinguishing between the response options "a lot" and very much". - inadequate measurement of patients with mild illness. 5of the 6 subscales have a strong floor effect, suggesting it may be less sensitive to changes in mild psoriasis.(33)

DLQI
- the unidimensionality has been questioned, that is, it calculates a total score from 5 scales but does not measure a unidimensional construct.(32) - DLQI was developed prior to the use of Rasch analysis. Twiss 2012 applied Rasch analysis to DLQI data to: determine whether the scale is unidimensional; assess its measurement properties; test the response format; and determine whether the measure exhibits differential item functioning by disease (atopic dermatitis versus psoriasis), gender, or age group. The authors used DLQI data from patients with psoriasis or atopic dermatitis, with data samples analysed for the 2 conditions combined and also separated. One issue identified was that large proportions of patients answered ‘‘not relevant’’ to several items. ‘‘Not relevant’’ responses are given the same score as the ‘‘not at all’’ response. This scoring method is an issue because patients who responded ‘‘not relevant’’ may actually have had severe illness. Overall, the results found issues with the scale, including misfitting items, differential item functioning by disease, age, and gender, disordered response thresholds (especially patients had trouble distinguishing between the response options “a lot” and “very much”), and inadequate measurement of patients with mild illness. For patients with psoriasis, the DLQI misfit the Rasch model indicating that it does not measure a unidimensional construct. The authors concluded that it may not be valid to compare scores for groups of patients whose profile differs in terms of age or gender. They recommended that a new measure of functional limitations in dermatology be developed using modern scaling techniques.(27) MCID ● Studies estimating the MCID of the DLQI have reported results varying from 3 to 5. ● An MCID of 5 is commonly cited, but this is based on a preliminary study published as an abstract. ● The most recent, comprehensive study found an MCID of 3.3. From a practical point of view, the authors recommended that the MCID should be 4 in inflammatory skin diseases. This was a longitudinal study: at stage 1, patients completed the DLQI and a disease severity global question; at stage 2, a global rating of change in QoL (Global Rating of Change Questionnaire) was added and used as an anchor to measure the MCID of the DLQI. 192 patients completed stage 1 and 107 completed stage 2. The mean DLQI score at stage 1 was 9.8 and at stage 2 was 7.4, with a mean change of 2.4 ($p < 0.0001$). Based on the responses to the Global Rating of Change Questionnaire, patients were divided into 4 categories: those having experienced no change, a small change, moderate change and large change. 31 patients experienced a ‘small change’ in their QoL (±3 and ±2) on the Global Rating of Change Questionnaire. The mean corresponding change in DLQI scores was 3.3 (SRM = 0.27; ES = 0.21), which was regarded as the approximate MCID of the DLQI scores. The mean DLQI scores in patients with ‘no change’, ‘moderate’ and ‘large’ change on the Global Rating of Change Questionnaire were 2.7 (n =23; SRM = 0.01, ES = 0.004), 4.4 (n = 25; SRM = 0.46, ES = 0.39) and 6 (n = 28; SRM = 0.69, ES = 0.67). (26) Comparison with other HRQoL measures Skindex Skindex-29 comprises 29 questions for dermatological disease in general covering burden of symptoms, functioning and emotional domains. Items are scored on a five-point scale from “never” to “all the time”. Skindex-29 has subsequently been updated by applying the Rasch model which resulted in a reduced version, Skindex-17. ● An observational, prospective, multicentre study (n=380) in Spain (Fernandez-Peñas 2012) compared 4 self-administered QoL instruments in patients aged > 18 years with mild to severe psoriasis attending dermatology clinics. Patients completed Skindex-29 (anchor) and a second instrument randomly selected from DLQI, PDI and SF-36. BSA and PASI. All subscales (symptoms, emotions, functioning) of Skindex-29 showed strong correlation with the global scores of all 3 of the other instruments (Spearman’s r=0.57−0.73, p<0.01). The symptoms subscale of Skindex-29 also showed a significant, albeit weaker, correlation with clinical severity on the PASI (Spearman’s r=0.20–0.35,

DLQI
p<0.05), with only PDI showing a similar correlation among the other 3 instruments. Skindex-29 exhibited a minimal floor and ceiling effect, whereas a substantial floor effect (suggesting reduced sensitivity in mild psoriasis) was seen with most subscales of the DLQI (5 of 6), SF-36 (5 of 8) and PDI (4 of 5). Skindex-29 showed strong correlations with the other three QoL instruments.(33)
● The UK NICE 2014 evidence update stated that the evidence suggests that in dermatology outpatients, Skindex-29 has good correlation with existing tools (the DLQI, the PDI, and the SF-36), and appears to have greater sensitivity to clinical severity than other instruments particularly in mild psoriasis. Although NICE did not specifically recommend Skindex-29 for assessment of quality of life, it noted the potential of this measure to address some of the issues with current tools. (10)
● A key advantage of Skindex versus DLQI is the greater sensitivity in mild psoriasis (which was defined as DLQI<7). However, this concern may be less relevant to populations with moderate-to-severe psoriasis.

BSA = body surface area; DLQI = Dermatology Life Quality Index; EQ-5D = EuroQoL-5D; ES = effect size; MCID = minimal clinically important difference; NICE = National Institute for Health and Care Excellence; PASI = Psoriasis Area and Severity Index; PDI = Psoriasis Disability Index; QoL = quality of life; RCTs = randomised controlled trials; SF-36 = Medical Outcome Study Short Form 36; SRM = standardised response mean; UK = United Kingdom

Table 18: DLQI in children

DLQI in children
CDQLI was developed to measure the impact of skin disease on QoL in children. The CDLQI comprises 10 questions regarding the impact of skin disease over the last week. The topics covered include symptoms, embarrassment, friendships, clothes, playing, sports, school, bullying, sleep and impact of treatment. The CDLQI has been validated for use in children aged 4–16 years, and is available as a text or a cartoon version. The scoring for each question is 'Very much' [Score = 3], 'Quite a lot' [2], 'Only a little' [1], 'Not at all' [0], 'Blank' [0]. The 10 individual question scores are summed to provide a total CDLQI score; the maximum possible score is 30, indicating maximum impact on QoL. The CDLQI scores are banded into the following severity bands: 0–1, no effect on QoL; 2–6, small effect; 7–12, moderate effect; 13–18, very large effect; 19–30, extremely large effect.(30) Strengths There is evidence of high internal consistency, test–retest reliability, responsiveness to change, and significant correlation with other subjective and objective measures. Limitations Rasch analysis has not been carried out and more information is needed concerning minimal clinically important difference. Summary of studies • Olsen 2016 conducted a meta-analysis of all published QoL scores for childhood skin conditions. The authors stated that CDLQI has been used in over 102 studies and is the most widely used dermatology-specific instrument for measuring QoL in children. They identified 6 studies that used the CDLQI in children with psoriasis. (30) •de Jager 2010 investigated whether disease severity scores correlated with QoL scores in patients ≤ 18 yrs. At baseline, the CDLQI questionnaire was completed and disease severity was assessed by PASI and PGA. 39 pts were included. The correlation coefficient between PASI and CDLQI was 0.47 (P =0.003), whereas the correlation coefficient between PGA and CDLQI was 0.51 (P =0.001). The authors concluded that "the correlation between disease severity scores and disease-related QoL in children with psoriasis is only moderate. Therefore, both clinical outcome parameters (PASI, PGA) and measures of QoL (CDLQI) should be included in adequate, patient-oriented clinical decision making." (31) • van Geel 2016 compared DLQI and CDLQI scores in pts with psoriasis aged 16-17 yrs (n = 56). There was a high correlation between DLQI and CDLQI scores (*r* = 0.90, P < 0.001). The mean DLQI score (5.41 ± 5.20) was lower than the mean CDLQI (6.61 ± 5.74) (P < 0.001). The difference (Δ 0.61) was mainly due to the low score for sexual difficulties in the DLQI (0.11 ± 0.49) and the high score concerning sleep in the CDLQI (0.71 ± 0.93) (48)

CDLQI = Children's Dermatology Life Quality Index; MCID = minimal clinically important difference; PASI = Psoriasis Area and Severity Index; PGA = Physician Global Assessment; QoL = quality of life

Table 19: Correlation between PASI and DLQI

Correlation between PASI and DLQI
A significant correlation has been shown between the 'Symptoms and feelings' and 'Treatment' subscales of DLQI with PASI.(33) ● Chaptini 2016 investigated the association between the DLQI and PASI of patients with psoriasis on biologic agents for two or more years (up to 6.5 years). This was a longitudinal, retrospective study conducted in a tertiary hospital in South Australia. PASI and DLQI were highly correlated over all time points (ρ = 0.50), P < 0.001. DLQI scores significantly decreased by 0.8 (95% CI: 0.30, 1.26) units per year from 12 months to 6.5 years, P = 0.002. After 12 months, PASI scores declined by 0.19 (95% CI: 0.13, 0.52) units per year, P = 0.24. The authors stated that this suggests that patients with psoriasis on biologics gain an improved QoL and PASI after biologic commencement, and their QoL remains high for many years following the commencement of biologic therapy.(34) ● Heredi 2014 analysed the relationship between EQ-5D, DLQI and PASI. They found strong correlation between DLQI and PASI (r_s = 0.81, p<0.05). EQ-5D showed a moderate correlation with DLQI and PASI (r^2 =-0.48 and -0.43, p<0.05). ● Mattei 2014 conducted a systematic review examining the correlation between DLQI and PASI in RCTs of biological agents in which both measures were assessed. Based on 13 RCTs, the % PASI improvement was strongly correlated with DLQI (r = 0.80) from baseline to weeks 10–16 of treatment. When grouped by mean % PASI reduction, agents that achieved PASI 75 demonstrated higher DLQI improvements than the agents that achieved lower PASI responses. In addition, achievement of PASI 75 was associated with improved DLQI (mean movement from DLQI band 3 to DLQI band 1). The authors concluded that mean PASI and DLQI correlate predictably in patients with moderate-to-severe CPP undergoing treatment with biological agents. PASI 75 translates to significant quality-of-life improvements in patients treated with these therapies. (35) ● Ali 2017 conducted a systematic review of the use of QoL instruments in RCTs for psoriasis found the correlations between PASI and absolute DLQI (R^2 = 0.49), and for percentage score changes the correlation was R^2 = 0.64.

DLQI = Dermatology Life Quality Index; MCID = minimal clinically important difference; PDI = Psoriasis Disability Index; RCT = randomised controlled trial

DERMATOLOGY LIFE QUALITY INDEX

DLQI

Hospital No: Date:
Name: Score:
Address: Diagnosis:

The aim of this questionnaire is to measure how much your skin problem has affected your life OVER THE LAST WEEK. Please tick ■ one box for each question.

1.	Over the last week, how **itchy**, **sore**, **painful** or **stinging** has your skin been?	Very much A lot A little Not at all	❒ ❒ ❒ ❒	
2.	Over the last week, how **embarrassed** or **self conscious** have you been because of your skin?	Very much A lot A little Not at all	❒ ❒ ❒ ❒	
3.	Over the last week, how much has your skin interfered with you going **shopping** or looking after your **home** or **garden**?	Very much A lot A little Not at all	❒ ❒ ❒ ❒	Not relevant ❒
4.	Over the last week, how much has your skin influenced the **clothes** you wear?	Very much A lot A little Not at all	❒ ❒ ❒ ❒	Not relevant ❒
5.	Over the last week, how much has your skin affected any **social** or **leisure** activities?	Very much A lot A little Not at all	❒ ❒ ❒ ❒	Not relevant ❒
6.	Over the last week, how much has your skin made it difficult for you to do any **sport**?	Very much A lot A little Not at all	❒ ❒ ❒ ❒	Not relevant ❒
7.	Over the last week, has your skin prevented you from **working** or **studying**?	Yes No	❒ ❒	Not relevant ❒
	If "No", over the last week how much has your skin been a problem at **work** or **studying**?	A lot A little Not at all	❒ ❒ ❒	
8.	Over the last week, how much has your skin created problems with your **partner** or any of your **close friends** or **relatives**?	Very much A lot A little Not at all	❒ ❒ ❒ ❒	Not relevant ❒
9.	Over the last week, how much has your skin caused any **sexual difficulties**?	Very much A lot A little Not at all	❒ ❒ ❒ ❒	Not relevant ❒
10.	Over the last week, how much of a problem has the **treatment** for your skin been, for example by making your home messy, or by taking up time?	Very much A lot A little Not at all	❒ ❒ ❒ ❒	Not relevant ❒

Please check you have answered EVERY question. Thank you.

Figure 6: DLQI questionnaire

Source: http://sites.cardiff.ac.uk/dermatology/quality-of-life/dermatology-quality-of-life-index-dlqi/ (Accessed 5 July 2017)

DLQI = Dermatology Life Quality Index.