## Journal

BioDrugs

## Title

Maintaining Clinical Freedom Whilst Achieving Value in Biologics Prescribing: An Integrated Cross-Specialty Consensus of UK Dermatologists, Rheumatologists and Gastroenterologists

## Authors

Tim Raine,1 Maria Angeliki Gkini,2 Peter M. Irving,3,4 Arvind Kaul,5 Eleanor Korendowych,6 Philip Laws,7 Amy C. Foulkes8

## Affiliations

1. Department of Gastroenterology, Addenbrooke’s Hospital, Cambridge University Hospitals NHS Foundation Trust, Cambridge, UK
2. Department of Dermatology, Barts Health NHS Trust, London, UK
3. IBD Centre, Department of Gastroenterology, Guy’s and St Thomas’ NHS Foundation Trust, London, UK
4. School of Immunology and Microbial Sciences, King’s College London, London, UK
5. Centre for Rheumatology, St George’s University Hospitals NHS Foundation Trust, London, UK
6. Department of Rheumatology, Royal United Hospitals Bath NHS Foundation Trust, Bath, UK
7. Department of Dermatology, The Leeds Teaching Hospitals NHS Trust, Leeds, UK
8. The Dermatology Centre, Salford Royal NHS Foundation Trust, NIHR Manchester Biomedical Research Centre, Manchester Academic Health Science Centre, Manchester, UK

## Corresponding author

Tim Raine (tim.raine@addenbrookes.nhs.uk)

Supplementary Table

Phase III, randomised controlled trials of biologics targeting IL-12/23, IL-23, IL-17 and integrins that have shown superiority versus TNF inhibitors

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Indication** | **Study** | **Treatment comparisons** | **Duration** | **Outcomes superior to TNFi** |
| Psoriasis | ACCEPT [1] | UST vs ETN | 12 weeks | PASI 75, PASI 90, PGA 0/1, PGA 0 |
| FIXTURE [2] | SEC vs ETN | 52 weeks | PASI 75, PASI 90, PASI 100, IGA 0/1 |
| IMMvent [3] | RIS vs ADA | 16 weeks | PASI 75, PASI 90, PASI 100, sPGA 0/1, sPGA 0, DLQI |
| reSURFACE 2 [4] | TIL vs ETN | 12 weeks | PASI 75, PASI 90, PASI 100, PGA 0/1, DLQI |
| UNCOVER-2 and -3 [5] | IXE vs ETN | 12 weeks | sPGA 0/1, sPGA 0, PASI 75, PASI 90, PASI 100, DLQI |
| VOYAGE 1 [6] | GUS vs ADA | 48 weeks | IGA 0/1, IGA 0, PASI 75, PASI 90, PASI 100, DLQI |
| VOYAGE 2 [7] | GUS vs ADA | 24 weeks | IGA 0/1, IGA 0, PASI 75, PASI 90, PASI 100, DLQI |
| PsA | SPIRIT-H2H [8] | IXE vs ADA | 24 weeks | ACR 50 and PASI 100 responses |
| Axial spondyloarthritis | COAST-V [9] | IXE vs ADA | 16 weeks | ASAS20, ASAS 40, BASDAI 50, MRI SPARCC spine score, MRI SPARCC sacroiliac joint score, SF-36 PCS, ASAS Health Index |
| Ulcerative colitis | VARSITY [10] | VDZ vs ADA | 52 weeks | Clinical remission, endoscopic improvement |

ACR, American College of Rheumatology; ADA, adalimumab; ASAS, Assessment in Ankylosing Spondylitis; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; DLQI, Dermatology Life Quality Index; ETN, etanercept; GUS, guselkumab; IBD, inflammatory bowel disease; IGA, Investigator’s Global Assessment; IL, interleukin; IXE, ixekizumab; MRI, magnetic resonance imaging; PASI, Psoriasis Area and Severity Index; (s)PGA, (static) Physician’s Global Assessment; PsA, psoriatic arthritis; RIS, risankizumab; SEC, secukinumab; SF-36 PCS, 36-Item Short Form Survey physical component score; SPARCC, Spondyloarthritis Research Consortium of Canada; TIL, tildrakizumab; TNF(i), tumour necrosis factor (inhibitor); UST, ustekinumab; VDZ, vedolizumab.

## References

1. Griffiths CEM, Strober BE, van de Kerkhof P, Ho V, Fidelus-Gort R, Yeilding N, et al. Comparison of Ustekinumab and Etanercept for Moderate-to-Severe Psoriasis. N Engl J Med. 2010;362:118–128.
2. Langley RG, Elewski BE, Lebwohl M, Reich K, Griffiths CEM, Papp K, et al. Secukinumab in plaque psoriasis - Results of two phase 3 trials. N Engl J Med. 2014;371:326–338.
3. Reich K, Gooderham M, Thaçi D, Crowley JJ, Ryan C, Krueger JG, et al. Risankizumab compared with adalimumab in patients with moderate-to-severe plaque psoriasis (IMMvent): a randomised, double-blind, active-comparator-controlled phase 3 trial. Lancet. 2019;394:576–586.
4. Reich K, Papp KA, Blauvelt A, Tyring SK, Sinclair R, Thaçi D, et al. Tildrakizumab versus placebo or etanercept for chronic plaque psoriasis (reSURFACE 1 and reSURFACE 2): results from two randomised controlled, phase 3 trials. Lancet. 2017;390:276–288.
5. Griffiths CEM, Reich K, Lebwohl M, Van De Kerkhof P, Paul C, Menter A, et al. Comparison of ixekizumab with etanercept or placebo in moderate-to-severe psoriasis (UNCOVER-2 and UNCOVER-3): Results from two phase 3 randomised trials. Lancet. 2015;386:541–551.
6. Blauvelt A, Papp KA, Griffiths CEM, Randazzo B, Wasfi Y, Shen YK, et al. Efficacy and safety of guselkumab, an anti-interleukin-23 monoclonal antibody, compared with adalimumab for the continuous treatment of patients with moderate to severe psoriasis: Results from the phase III, double-blinded, placebo- and active comparator–controlled VOYAGE 1 trial. J Am Acad Dermatol. 2017;76:405–417.
7. Reich K, Armstrong AW, Foley P, Song M, Wasfi Y, Randazzo B, et al. Efficacy and safety of guselkumab, an anti-interleukin-23 monoclonal antibody, compared with adalimumab for the treatment of patients with moderate to severe psoriasis with randomized withdrawal and retreatment: Results from the phase III, double-blind, placebo- and active comparator–controlled VOYAGE 2 trial. J Am Acad Dermatol. 2017;76:418–431.
8. Mease PJ, Smolen JS, Behrens F, Nash P, Liu Leage S, Li L, et al. A head-to-head comparison of the efficacy and safety of ixekizumab and adalimumab in biological-naïve patients with active psoriatic arthritis: 24-week results of a randomised, open-label, blinded-assessor trial. Ann Rheum Dis. 2020;79:123–131.
9. van der Heijde D, Cheng-Chung Wei J, Dougados M, Mease P, Deodhar A, Maksymowych WP, et al. Ixekizumab, an interleukin-17A antagonist in the treatment of ankylosing spondylitis or radiographic axial spondyloarthritis in patients previously untreated with biological disease-modifying anti-rheumatic drugs (COAST-V): 16 week results of a phase 3 randomised, double-blind, active-controlled and placebo-controlled trial. Lancet. 2018;392:2441–2451.
10. Vedolizumab versus Adalimumab for Moderate-to-Severe Ulcerative Colitis. N Engl J Med. 2019;381:1215–1226.

Literature Search

# Objectives

* To review available literature and relevant guidelines in order to support clinical opinion and guide the modified Delphi consensus process

# Key Research Questions

## Clinical Freedom

* 1. What is the principle of “clinical freedom”, and how does it differ from clinical judgement?
  2. What is the importance of the principle of “clinical freedom” to clinicians, patients and to the healthcare system?
  3. To what extent would greater understanding of the Biologic Commissioning Framework permit greater clinical freedom?
  4. Are population-based pathways always applicable to individual patient-level treatment decisions? If not, which patient factors should be considered when deviating from the pathway?

## Value of Biologics

* 1. What is the difference between “value” and “price”, and how should these factor into patient-level treatment decisions for psoriasis, PsA, and IBD?
  2. Which drug-related factors can impart additional value on both the patient with psoriasis, PsA, and/or IBD and the healthcare system?
  3. What added value can novel biologics provide for patients with psoriasis, PsA, and/or IBD, beyond that offered by a TNFi? Is this specific to certain patient types or does it apply to the full patient spectrum?
  4. Does any additional value to patients with psoriasis, PsA, and/or IBD offered by novel biologics affect their positioning in the treatment pathway relative to TNFis?

## Current Practices in the Biologic Era

* 1. Which patient factors should impact choice of biologic prescription for psoriasis, PsA, or IBD (e.g. disease severity, location, duration, prior drug exposure, comorbidities, previous AEs or family history thereof, patient preferences and beliefs)?
  2. Has availability of newer biologic options changed prescribing patterns in psoriasis, PsA, and IBD? If so, how? What effect has this had on patient outcomes?
  3. To what extent is there room for variation in interpretation of NICE guidelines for biologic prescription in psoriasis, PsA, and IBD, and how well does this align with the Biologic Commissioning Framework?
  4. At what point in the treatment of psoriasis, PsA, and IBD should a clinician consider a switch from one biologic class to another? Which factors should go into making this decision?

# Process

A literature search was performed ahead of the e-survey and group meeting. Search terms were identified and collated from PubMed Central and the European, UK national and NICE clinical guidelines. Articles that did not contribute to the key research questions were excluded. Including the NICE clinical guidelines, 144 unique references were summarised into key themes and used to highlight research gaps or considerations.

*Supplementary Table 1: Search Terms Used in PubMed Central*

|  |  |  |
| --- | --- | --- |
| Key research question | Search query | Hits after exclusions |
| 1. *Clinical freedom* | | |
| * 1. What is the principle of “clinical freedom”, and how does it differ from clinical judgement? | (("clinical freedom") OR (“clinical freedom” AND "clinical judgement")) | 62 |
| * 1. What is the importance of the principle of “clinical freedom” to clinicians, patients and to the healthcare system? | (“clinical freedom”) AND ((relevance) OR (importance)) AND ((clinicians) OR (physicians) OR (doctors) OR (patients) OR (“healthcare system”)) NOT (prostate) | 14 |
| * 1. To what extent would greater understanding of the Biologic Commissioning Framework permit greater clinical freedom? | N/A | – |
| * 1. Are population-based pathways always applicable to individual patient-level treatment decisions? If not, which patient factors should be considered when deviating from the pathway? | (biologic) AND (((population) AND (pathway)) OR ("patient factors") OR ("treatment decisions") OR ("prescribing decisions") OR ("individualized care") OR ("personalized care") OR ("patient-centric")) AND ((psoriasis) OR (PsA) OR (“psoriatic arthritis”) OR (IBD) OR (“inflammatory bowel disease”) OR (“Crohn’s disease”) OR (“ulcerative colitis”)) NOT (prostate) | 11 |
| 1. *Value of biologics* | | |
| * 1. What is the difference between “value” and “price”, and how should these factor into patient-level treatment decisions for psoriasis, PsA, and IBD? | (biologic) AND ((drug) OR (healthcare) OR (medicine) OR (treatment) OR (therapy)) AND ((value) AND (price) AND (defined)) NOT (cost) NOT (analysis) | 2 |
| * 1. Which drug-related factors can impart additional value on both the patient with psoriasis, PsA, and/or IBD and the healthcare system? (e.g. clinical efficacy, patient adherence, safety, tolerability and immunogenicity profiles, dosing regimen) | ((drug) OR (healthcare) OR (medicine) OR (treatment) OR (therapy)) AND (value) AND ("healthcare system") AND (factors) AND ((psoriasis) OR (PsA) OR (“psoriatic arthritis”) OR (IBD) OR (“inflammatory bowel disease”) OR (“Crohn’s disease”) OR (“ulcerative colitis”)) NOT (prostate) | 10 |
| * 1. Can novel biologics add value for patients with psoriasis, PsA, and/or IBD beyond that offered by a TNFi? Is this specific to certain patient types or does it apply to the full patient spectrum? | ((IL-17 inhibitor) OR (anti-IL-17) OR (ixekizumab) OR (Taltz) OR (secukinumab) OR (Cosentyx) OR (brodalumab) OR (Kyntheum) OR (IL-12/23 inhibitor) OR (anti-IL-12/23) OR (ustekinumab) OR (Stelara) OR (IL-23 inhibitor) OR (anti-IL-23) OR (guselkumab) OR (Tremfya) OR (risankizumab) OR (Skyrizi) OR (tildrakizumab) OR (Ilumetri) OR (Ilumya) OR (“novel biologics”)) AND (value) AND ((psoriasis) OR (PsA) OR (“psoriatic arthritis”) OR (IBD) OR (“inflammatory bowel disease”) OR (“Crohn’s disease”) OR (“ulcerative colitis”)) NOT (prostate) | 11 |
| * 1. Does any additional value to patients with psoriasis, PsA, and/or IBD offered by novel biologics affect their positioning in the treatment pathway relative to TNFis? | ((IL-17 inhibitor) OR (anti-IL-17) OR (ixekizumab) OR (Taltz) OR (secukinumab) OR (Cosentyx) OR (brodalumab) OR (Kyntheum) OR (IL-12/23 inhibitor) OR (anti-IL-12/23) OR (ustekinumab) OR (Stelara) OR (IL-23 inhibitor) OR (anti-IL-23) OR (guselkumab) OR (Tremfya) OR (risankizumab) OR (Skyrizi) OR (tildrakizumab) OR (Ilumetri) OR (“novel biologics”)) AND ((value) OR (additional benefits)) AND (position) AND ((psoriasis) OR (PsA) OR (“psoriatic arthritis”) OR (IBD) OR (“inflammatory bowel disease”) OR (“Crohn’s disease”) OR (“ulcerative colitis”)) NOT (prostate) | 0 |
| 1. *Current practices in the biologic era* | | |
| * 1. Which patient factors should impact choice of TNFi vs. novel biologic prescription for psoriasis, PsA, or IBD (e.g. disease severity, location, duration, prior drug exposure, comorbidities, previous AEs or family history thereof, patient preferences and beliefs)? | ((TNFi) OR (TNF inhibitor) OR (anti-TNF)) AND (patient) AND ((suitability) OR (suitable) OR (appropriate)) AND ((psoriasis) OR (PsA) OR (“psoriatic arthritis”) OR (IBD) OR (“inflammatory bowel disease”) OR (“Crohn’s disease”) OR (“ulcerative colitis”)) NOT (prostate) | 23 |
| * 1. Has TNFi biosimilar availability changed prescribing patterns in psoriasis, PsA, and IBD? If so, how? What effect has this had on patient outcomes? | (biosimilars) AND (("patient outcomes") OR ("prescribing patterns") OR ("prescribing habits")) AND ((psoriasis) OR (PsA) OR (“psoriatic arthritis”) OR (IBD) OR (“inflammatory bowel disease”) OR (“Crohn’s disease”) OR (“ulcerative colitis”)) NOT (prostate) | 7 |
| * 1. To what extent is there room for variation in interpretation of NICE guidelines for biologic prescription in psoriasis, PsA, and IBD, and how well does this align with the Biologic Commissioning Framework on biosimilar prescription? | N/A | – |
| * 1. At what point in the treatment of psoriasis, PsA, and IBD should a clinician consider a switch from one biologic class to another, and which factors should go into making this decision? (e.g. time on therapy, clinical response, anti-drug antibodies, adverse events, unit cost, potential costs to the healthcare system, patient satisfaction, comorbidity development) | ((TNFi) OR (TNF inhibitor) OR (anti-TNF) OR (biosimilar) OR (biologic)) AND (switch) AND (class) AND ((psoriasis) OR (PsA) OR (“psoriatic arthritis”) OR (IBD) OR (“inflammatory bowel disease”) OR (“Crohn’s disease”) OR (“ulcerative colitis”)) NOT (prostate) | 4 |

# List of Publications Retrieved

Akai, M. (2002). Evidence-based medicine for orthopedic practice. *Journal of Orthopaedic Science*, Vol. 7, pp. 731–742.

Al Omari, M., *et al.* (2009). Evidence-based medicine among hospital doctors in Jordan: Awareness, attitude and practice. *Journal of Evaluation in Clinical Practice*, *15*(6), 1137–1141.

Allocca M, *et al.* (2018). Biologic Therapies in Ulcerative Colitis: Primi Inter Pares? *Curr Drug Targets*, *19*(7), 748–756.

Almario CV, *et al.* (2018). Optimizing Selection of Biologics in Inflammatory Bowel Disease: Development of an Online Patient Decision Aid Using Conjoint Analysis. *Am J Gastroenterol*, *113*(1), 58–71.

Amin, M., *et al.* (2018). Choosing First-Line Biologic Treatment for Moderate-to-Severe Psoriasis: What Does the Evidence Say? *American Journal of Clinical Dermatology*, *19*(1).

Atteno, M., *et al.* (2014). The use of TNF-α blockers in psoriatic arthritis patients with latent tuberculosis infection. *Clinical Rheumatology*, *33*(4), 543–547.

Ayala, F., *et al.* (2015). Efficacy, tolerability and safety of switching from etanercept to infliximab for the treatment of moderate-to-severe psoriasis: A multicenter, open-label trial (TANGO). *The Journal of Dermatological Treatment*, *26*(4), 304–311.

Beigel, F., *et al.* (2009). Severe Legionella pneumophila pneumonia following infliximab therapy in a patient with Crohn’s disease. *Inflammatory Bowel Diseases*, *15*(8), 1240–1244.

Berger, T., *et al.* (2018). Management of multiple sclerosis patients in central European countries: current needs and potential solutions. *Therapeutic Advances in Neurological Disorders*, *11*, 1–12.

Bogod, D. G. (2009). Off-licence use of medicines is bad medicine flying the flag of clinical freedom. *International Journal of Obstetric Anesthesia*, *18*(3), 250–252.

Boyd, G. (2014). Clinical judgement and the emotions. *Internal Medicine Journal*, *44*(7), 704–706.

Burls, A. (2010). On the resuscitation of clinical freedom. *BMC Health Services Research*, *10*.

Chang, J., & Girgis, L. (2007). Clinical use of anti-TNF-α biological agents: A guide for GPs. *Australian Family Physician*, *36*(12), 1035–1038.

Chapman, M. A., *et al.* (2018). The Role of Biosimilars in Patient Access to Therapeutic Antibodies for Immune Mediated Inflammatory Diseases. *Current Pharmaceutical Design*, *23*(44), 6779–6783.

Cline, A., *et al.* (2016). Current status and future prospects for biologic treatments of psoriasis. *Expert Review of Clinical Immunology*, Vol. 12, pp. 1273–1287.

Coates, L. C., *et al.* (2012) The 2012 BSR and BHPR guideline for the treatment of psoriatic arthritis with biologics. *Rheumatology, 52*(10), 1754–1757.

Coates, L. C., *et al.* (2017). New GRAPPA and EULAR recommendations for the management of psoriatic arthritis. *Rheumatology (United Kingdom)*, Vol. 56, pp. 1251–1253.

Coates, L. C., *et al.* (2016). Group for Research and Assessment of Psoriasis and Psoriatic Arthritis 2015 Treatment Recommendations for Psoriatic Arthritis. *Arthritis & Rheumatology*, *68*(5), 1060–1071.

Conroy, M., & Shannon, W. (1995). Clinical guidelines: Their implementation in general practice. *British Journal of General Practice*, *45*(396), 371–375.

Dávila-Seijo, P., *et al.* (2016). Survival of classic and biological systemic drugs in psoriasis: results of the BIOBADADERM registry and critical analysis. *Journal of the European Academy of Dermatology and Venereology : JEADV*, *30*(11), 1942–1950.

de Souza, S., *et al.* (2017). Scintigraphy for detecting tumour necrosis factor-α on the skin of patients with psoriatic arthritis. *Scandinavian Journal of Rheumatology*, *46*(5), 377–380.

Decock, A., *et al.* (2017). Sarcoidosis-Like Lesions: Another Paradoxical Reaction to Anti-TNF Therapy? *Journal of Crohn’s & Colitis*, *11*(3), 378–383.

DeVoe, J., *et al.* (2002). Does career dissatisfaction affect the ability of family physicians to deliver high-quality patient care? *Journal of Family Practice*, *51*(3), 223–228.

Dini, V., *et al.* (2017). Psoriatic arthritis prevalence in the clinical practice of dermatologists in North-West Tuscany centers of excellence: a screening experience. *Giornale Italiano Di Dermatologia e Venereologia : Organo Ufficiale, Societa Italiana Di Dermatologia e Sifilografia*, *152*(1), 24–27.

Dolinar, R., *et al.* (2019, July 4). The non-medical switching of prescription medications. *Postgraduate Medicine*, Vol. 131, pp. 335–341.

Dreesen E, V *et al.* (2018). Evidence to Support Monitoring of Vedolizumab Trough Concentrations in Patients With Inflammatory Bowel Diseases. *Clin Gastroenterol Hepatol*, *16*(12), 1937–1946.

Duffin, K. C., *et al.* (2014). Patient satisfaction with treatments for moderate-to-severe plaque psoriasis in clinical practice. *The British Journal of Dermatology*, *170*(3), 672–680.

Egeberg, A., *et al.* (2018). Safety, efficacy and drug survival of biologics and biosimilars for moderate-to-severe plaque psoriasis. *British Journal of Dermatology*, *178*(2), 509–519.

Esposito, M., *et al.* (2012). Efficacy and safety of subcutaneous anti-tumor necrosis factor-alpha agents, etanercept and adalimumab, in elderly patients affected by psoriasis and psoriatic arthritis: an observational long-term study. *Dermatology (Basel, Switzerland)*, *225*(4), 312–319.

Freddi, G., & Romàn-Pumar, J.L. (2011). Evidence-based Medicine: What It Can and Cannot Do. *Annali Dell’Istituto Superiore Di Sanita*, *47*(1), 22–25.

Galván-Banqueri M., *et al.* (2013). Biological treatments for moderate-to-severe psoriasis: indirect comparison. *J Clin Pharm Ther*, *38*(2), 121–130.

Geynisman, D. M., *et al.* (2017). Biosimilar biologic drugs: a new frontier in medical care. *Postgraduate Medicine*, *129*(4), 460–470.

Ginsburg, G. S., & Phillips, K. A. (2018). *Health Aff (Millwood)*. *37*(5), 694–701.

Girolomoni, G., *et al.* (2017). The role of IL-23 and the IL-23/TH 17 immune axis in the pathogenesis and treatment of psoriasis. *Journal of the European Academy of Dermatology and Venereology : JEADV*, *31*(10), 1616–1626.

González-Lama, Y., *et al.* (2016). Timing of thiopurine or anti-TNF initiation is associated with the risk of major abdominal surgery in crohn’s disease: A retrospective cohort study. *Journal of Crohn’s and Colitis*, *10*(1), 55–60.

Gooderham, M. J., *et al.* (2018). Shifting the focus - the primary role of IL-23 in psoriasis and other inflammatory disorders. *Journal of the European Academy of Dermatology and Venereology : JEADV*, *32*(7), 1111–1119.

Gostin, L. O. (2007). Abortion politics: clinical freedom, trust in the judiciary, and the autonomy of women. *JAMA*, *298*(13), 1562–1564.

Hampton, J. R. (1983). The end of clinical freedom. *BMJ*, *287*(6401), 1237–1238.

Hampton, J. R. (1997). Evidence-based medicine, practice variations and clinical freedom. *Journal of Evaluation in Clinical Practice*, Vol. 3, pp. 123–131.

Hampton, J. R. (2011). The end of clinical freedom. *International Journal of Epidemiology*, Vol. 40, pp. 848–849.

Hampton, J. (2011). Commentary: The need for clinical freedom. *International Journal of Epidemiology*, Vol. 40, pp. 849–852.

Hampton, J. R. (2002). Evidence-Based Medicine, Opinion-Based Medicine, and Real-World Medicine. *Perspectives in Biology and Medicine*, *45*(4), 549–568.

Hanning, M., & Spångberg, U. W. (2000). Maximum waiting time - A threat to clinical freedom? Implementation of a policy to reduce waiting times. *Health Policy*, *52*(1), 15–32.

Hart, R. I., *et al.* (2015). Young people’s decisions about biologic therapies: who influences them and how? *Rheumatology (Oxford, England)*, *54*(7), 1294–1301.

Healy, D., *et al.* (2013). Data based medicine and clinical judgement. *International Journal of Risk and Safety in Medicine*, Vol. 25, pp. 111–121.

Hendrix, N., *et al.* (2018). Cost-effectiveness of targeted pharmacotherapy for moderate to severe plaque psoriasis. *Journal of Managed Care and Specialty Pharmacy*, *24*(12), 1210-1217C.

Hoffman, M. B., *et al.* (2016). Current challenges and emerging drug delivery strategies for the treatment of psoriasis. *Expert Opinion on Drug Delivery*, *13*(10), 1461–1473.

Hopper, L., *et al.* (2011). A qualitative investigation of the views of primary care dentists on participating in prospective studies in the North-West of England. *British Dental Journal*, *210*(11).

Hutton, J. L., *et al.* (2008). Ethical issues in implementation research: a discussion of the problems in achieving informed consent. *Implementation Science : IS*, *3*, 52.

Iannone, F., *et al.* (2018). Drug survival and effectiveness of ustekinumab in patients with psoriatic arthritis. Real-life data from the biologic Apulian registry (BIOPURE). *Clinical Rheumatology*, *37*(3), 667–675. https://doi.org/10.1007/s10067-018-3989-2

Johnson, F. R., *et al.* (2010). Are gastroenterologists less tolerant of treatment risks than patients? Benefit-risk preferences in Crohn’s disease management. *Journal of Managed Care Pharmacy : JMCP*, *16*(8), 616–628.

Johnson, M. R., *et al.* (2015). Physician Non-adherence to Colonoscopy Interval Guidelines in the Veterans Affairs Healthcare System. *Gastroenterology*, *149*(4), 938–951.

Johnson, S. L., *et al.* (2015). Biological and steroid use in relationship to quality measures in older patients with inflammatory bowel disease: a US Medicare cohort study. *BMJ Open*, *5*(9), e008597.

Joyce, C. R., & Hammond, K. R. (1983). Improving clinical judgement. *British Journal of Rheumatology*, *22*(3 Suppl), 14–17.

Kannan, D., & Levitt, H. M. (2017). Self-criticism in therapist training: A grounded theory analysis. *Psychotherapy Research : Journal of the Society for Psychotherapy Research*, *27*(2), 201–214.

Karthikeyan, G., & Pais, P. (2010). Clinical judgement & evidence-based medicine: Time for reconciliation. *Indian Journal of Medical Research*, Vol. 132, pp. 623–626.

Kee, F., *et al.* (2000). Stewardship or clinical freedom? Variations in dialysis decision making. *Nephrology Dialysis Transplantation*, *15*(10), 1647–1657.

Khan, N., *et al.* (2012). Long-term oral mesalazine adherence and the risk of disease flare in ulcerative colitis: Nationwide 10-year retrospective cohort from the veterans affairs healthcare system. *Alimentary Pharmacology and Therapeutics*, *36*(8), 755–764.

Kienle, G. S., & Kiene, H. (2011). Clinical judgement and the medical profession. *Journal of Evaluation in Clinical Practice*, *17*(4), 621–627.

Kravitz, R. L., *et al.* (2008). N-of-1 trials of expensive biological therapies: A third way? *Archives of Internal Medicine*, *168*(10), 1030–1033.

Kulier, R., *et al.* (2008). Five steps from evidence to effect: exercising clinical freedom to implement research findings. *BJOG : An International Journal of Obstetrics and Gynaecology*, *115*(10), 1197–1202.

Lamb, C. A., *et al.* (2019). British Society of Gastroenterology consensus guidelines on the management of inflammatory bowel disease in adults. *Gut*, *68*, s1–s106.

Li, J., *et al.* (2016). Profiles of Lamina Propria T Helper Cell Subsets Discriminate between Ulcerative Colitis and Crohn’s Disease. *Inflammatory Bowel Diseases*, *22*(8), 1779–1792.

Long, J., *et al.* (2013). What do clinical optometrists like about their job? *Clinical and Experimental Optometry*, *96*(5), 460–466.

Lubrano E, *et al.* (2011). The effectiveness of a biologic agent on axial manifestations of psoriatic arthritis. A twelve months observational study in a group of patients treated with etanercept. *Clin Exp Rheumatol*, *29*(1), 80–84.

Lysaght, T., *et al.* (2013). Oversight for clinical uses of autologous adult stem cells: Lessons from international regulations. *Cell Stem Cell*, Vol. 13, pp. 647–651.

MacKinnon, R. J. (2007). Evidence based medicine methods (part 1): the basics. *Pediatric Anesthesia*, *17*(10), 918–923.

Macnaughton, R. J. (1998). Evidence and clinical judgement. *Journal of Evaluation in Clinical Practice*, *4*(2), 89–92.

Masarwa R, et al. (2018). Prenatal Exposure to Acetaminophen and Risk for Attention Deficit Hyperactivity Disorder and Autistic Spectrum Disorder: A Systematic Review, Meta-Analysis, and Meta-Regression Analysis of Cohort Studies. *American Journal of Epidemiology, 187*(8), 1817–1827.

Maynard, A. (2011). Commentary: Clinical freedom is dead and no one need regret its passing. *International Journal of Epidemiology*, Vol. 40, pp. 858–859.

McCarthy, M. W., *et al.* (2018). Off the Charts: *Medical documentation and selective redaction in the age of transparency*. *Perspectives in Biology and Medicine*, *61*(1), 118–129.

Melmed, G. Y., *et al.* (2010). The Appropriateness of Concomitant Immunomodulators With Anti–Tumor Necrosis Factor Agents for Crohn’s Disease: One Size Does Not Fit All. *Clinical Gastroenterology and Hepatology*, *8*(8), 655–659.

Mendenhall, N. P., *et al.* (2014). Five-year outcomes from 3 prospective trials of image-guided proton therapy for prostate cancer. *International Journal of Radiation Oncology, Biology, Physics*, *88*(3), 596–602.

Menter, A., *et al.* (2016). Drug survival of biologic therapy in a large, disease-based registry of patients with psoriasis: results from the Psoriasis Longitudinal Assessment and Registry (PSOLAR). *Journal of the European Academy of Dermatology and Venereology : JEADV*, *30*(7), 1148–1158.

Miners, A. H., *et al.* (2005). Comparing estimates of cost effectiveness submitted to the National Institute for Clinical Excellence (NICE) by different organisations: Retrospective study. *British Medical Journal*, *330*(7482), 65–68.

Miyagawa, I., *et al.* (2018). Precision medicine using different biological DMARDs based on characteristic phenotypes of peripheral T helper cells in psoriatic arthritis. *Rheumatology*, (July), 1–9.

Monaghan, N. (1999). Human nature and clinical freedom, barriers to evidence-based practice? *British Dental Journal*, *186*(5), 208–209.

Narayanan, S. (2016). Demonstrating the value of medicines: evolution of value equation and stakeholder perception of uncertainties. *Journal of Market Access & Health Policy*, *4*(1), 31670.

Nast, A., *et al.* (2018). S3 guideline for the treatment of psoriasis vulgaris, update – short version part 2 – special patient populations and treatment situations. *JDDG - Journal of the German Society of Dermatology*, Vol. 16, pp. 806–814.

Nguyen, E., *et al.* (2016). Impact of non-medical switching on clinical and economic outcomes, resource utilization and medication-taking behavior: A systematic literature review. *Current Medical Research and Opinion*, Vol. 32, pp. 1281–1290.

NHS England. (2017). *Commissioning framework for biological medicines (including biosimilar medicines)*. Available at: <https://www.england.nhs.uk/wp-content/uploads/2017/09/biosimilar-medicines-commissioning-framework.pdf>. Last accessed 06 August 2020.

NICE. (2008). *Adalimumab for the treatment of adults with psoriasis*. Available at: [www.nice.org.uk/guidance/ta146](http://www.nice.org.uk/guidance/ta146). Last accessed 06 August 2020.

NICE. (2017). *Certolizumab pegol and secukinumab for treating active psoriatic arthritis after inadequate response to DMARDs*. Available at: [www.nice.org.uk/guidance/ta445](http://www.nice.org.uk/guidance/ta445). Last accessed 06 August 2020.

NICE. (2009). *Costing statement : Ustekinumab for the treatment of adults with moderate to severe psoriasis*. *103*(September 2009), 1–4. Available at: www.nice.org.uk/guidance/ta180

NICE. (2019). *Crohn’s disease: management NICE guideline*. Available at: [www.nice.org.uk/guidance/ng129](http://www.nice.org.uk/guidance/ng129). Last accessed 06 August 2020.

NICE. (2006). *Etanercept and efalizumab for the treatment of adults with psoriasis*. Available at: <https://www.nice.org.uk/guidance/TA103>. Last accessed 06 August 2020.

NICE. (2011). *Golimumab for the treatment of psoriatic arthritis*. Available at: [www.nice.org.uk/guidance/ta220](http://www.nice.org.uk/guidance/ta220). Last accessed 06 August 2020.

NICE. (2018). *Guselkumab for treating moderate to severe plaque psoriasis*. Available at: [www.nice.org.uk/guidance/ta521](http://www.nice.org.uk/guidance/ta521). Last accessed 06 August 2020.

NICE. (2008). *Infliximab for the treatment of adults with psoriasis*. Available at: [www.nice.org.uk/guidance/ta134](http://www.nice.org.uk/guidance/ta134). Last accessed 06 August 2020.

NICE. (2018). *Ixekizumab for treating active psoriatic arthritis after inadequate response to DMARDs*. Available at: [www.nice.org.uk/guidance/ta537](http://www.nice.org.uk/guidance/ta537). Last accessed 06 August 2020.

NICE. (2012). *Psoriasis: assessment and management Clinical guideline*. Available at: [www.nice.org.uk/guidance/cg153](http://www.nice.org.uk/guidance/cg153). Last accessed 06 August 2020.

NICE. (2015). *Secukinumab for treating moderate to severe plaque psoriasis*. Available at: [www.nice.org.uk/guidance/ta350](http://www.nice.org.uk/guidance/ta350). Last accessed 06 August 2020.

NICE. (n.d.). Systemic biological therapy for psoriasis - NICE Pathways. Available at: <https://pathways.nice.org.uk/pathways/psoriasis#path=view%3A/pathways/psoriasis/systemic-biological-therapy-for-psoriasis.xml&content=view-index>. Last accessed 06 August 2020.

NICE. (2019). *Tildrakizumab for treating moderate to severe plaque psoriasis Technology appraisal guidance*. Available at: [www.nice.org.uk/guidance/ta575](http://www.nice.org.uk/guidance/ta575). Last accessed 06 August 2020.

NICE. (2019). *Ulcerative colitis: management NICE guideline*. Available at: [www.nice.org.uk/guidance/ng130](http://www.nice.org.uk/guidance/ng130). Last accessed 06 August 2020.

NICE. (2015). *Ustekinumab for treating active psoriatic arthritis. Available at:* <https://www.nice.org.uk/guidance/ta340>.Last accessed 06 August 2020.

NICE. (2019). Risankizumab for treating moderate to severe plaque psoriasis. Available at: <https://www.nice.org.uk/guidance/ta596>. Last accessed 06 August 2020.

NICE. (2019). *Ustekinumab for moderately to severely active Crohn’s disease after previous treatment*. Available at: <https://www.nice.org.uk/guidance/ta456>. Last accessed 06 August 2020.

NICE. (2019). *Etanercept, infliximab and adalimumab for the treatment of psoriatic arthritis*. Available at: <https://www.nice.org.uk/guidance/ta199>. Last accessed 06 August 2020.

NICE. (2019). *Vedolizumab for treating moderately to severely active ulcerative colitis*. Available at: <https://www.nice.org.uk/guidance/ta342>. Last accessed 06 August 2020.

NICE. (2018). *Infliximab, adalimumab and golimumab for treating moderately to severely active ulcerative colitis after the failure of conventional therapy*. Available at: <https://www.nice.org.uk/guidance/ta329>. Last accessed 06 August 2020.

NICE. (2019). *Vedolizumab for treating moderately to severely active Crohn’s disease after prior therapy*. <https://www.nice.org.uk/guidance/ta352>. Last accessed 06 August 2020.

NICE. (2018). *Brodalumab for treating moderate to severe plaque psoriasis*. Available at: [www.nice.org.uk/guidance/ta511](http://www.nice.org.uk/guidance/ta511). Last accessed 06 August 2020.

NICE. (2019). *Ixekizumab for treating moderate to severe plaque psoriasis*. Available at: <https://www.nice.org.uk/guidance/ta442>. Last accessed 06 August 2020.

Oskouei, S. T. (2017). Following the Biosimilar Breadcrumbs: When Health Systems and Manufacturers Approach Forks in the Road. *Journal of Managed Care & Specialty Pharmacy*, *23*(12), 1245–1248.

Parker, M. (2005). False dichotomies: EBM, clinical freedom, and the art of medicine. *Medical Humanities*, *31*(1), 23–30.

Parker, M. (2011). Commentary: The clinical freedom worth Having-commentary on Hampton (1983). *International Journal of Epidemiology*, Vol. 40, pp. 853–855.

Peters, R., *et al.* (2020). An investigation of antihypertensive class, dementia, and cognitive decline: A meta-analysis. *Neurology*, *94*(3), e267–e281.

Piaserico S, *et al.* (2017). Adalimumab is a safe option for psoriasis patients with concomitant hepatitis B or C infection: a multicentre cohort study of 37 patients and review of the literature. *J Eur Acad Dermatol Venereol*, *31*(11), 1853–1859.

Porter, M. E. (2010). What is value in health care? *New England Journal of Medicine*, Vol. 363, pp. 2477–2481.

Prieto-Pérez, R., *et al.* (2015). The polymorphism rs763780 in the IL-17F gene is associated with response to biological drugs in patients with psoriasis. *Pharmacogenomics*, *16*(15), 1723–1731.

Puig, L., *et al.* (2015). Biosimilars in Dermatology: Current Situation (Part II). *Actas Dermo-Sifiliograficas*, Vol. 106, pp. 550–554.

Puig, L., *et al.* (2015). Biosimilares en dermatología. Situación actual (parte i). *Actas Dermo-Sifiliográficas*, *106*(7), 545–549.

Rawlins, M. D. (2011). Commentary: the death of clinical freedom. *International Journal of Epidemiology*, *40*(4), 859–861.

Razanskaite, V., *et al.* (2017). Biosimilar Infliximab in Inflammatory Bowel Disease: Outcomes of a Managed Switching Programme. *Journal of Crohn’s & Colitis*, *11*(6), 690–696.

Rompas, S., *et al.* (2015). Demonstrating Value for Biosimilars: A Conceptual Framework. *American Health & Drug Benefits, 8*(3),129–139.

Sacristán, J. A., & Avendaño-Solá, C. (2015). On heterogeneity of treatment effects and clinical freedom. *International Journal of Clinical Practice*, *69*(1), 6–8.

Sacristn, J. A., *et al.* (2010). Health economics: The start of clinical freedom. *BMC Health Services Research*, *10*.

Saraceno R, *et al.* (2013). High density cholesterol level as predictor of clinical response to anti-TNF-alpha therapy in psoriatic patients. *J Biol Regul Homeost Agents*, *27*(3), 903–908.

Schimpf, K. (1994). Should clinical freedom be constrained in the name of self-sufficiency? *Blood Coagulation and Fibrinolysis*, *5*(Suppl. 4), S57–S50.

Schmitt, H., *et al.* (2019). Expansion of IL-23 receptor bearing TNFR2+ T cells is associated with molecular resistance to anti-TNF therapy in Crohn’s disease. *Gut*, *68*(5), 814–828.

Schnell-Inderst, P., *et al.* (2011). Individual health services. *GMS Health Technology Assessment*, *7*, Doc05.

Schulze-Koops, H., & Skapenko, A. (2017). Biosimilars in rheumatology: A review of the evidence and their place in the treatment algorithm. *Rheumatology (Oxford, England)*, Vol. 56, pp. iv30–iv48.

Shah, V. V., *et al.* (2018). Comparison of guidelines for the use of TNF inhibitors for psoriasis in the United States, Canada, Europe and the United Kingdom: a critical appraisal and comprehensive review. *Journal of Dermatological Treatment*, Vol. 29, pp. 586–592.

Sipeki, N., *et al.* (2015). Prevalence, significance and predictive value of antiphospholipid antibodies in Crohn’s disease. *World Journal of Gastroenterology*, *21*(22), 6952–6964.

Siriwardena, A. N. (1995). Clinical guidelines in primary care: a survey of general practitioners’ attitudes and behaviour. *The British Journal of General Practice : The Journal of the Royal College of General Practitioners*, *45*(401), 643–647.

Smith, C. H., *et al.* (2017). British Association of Dermatologists guidelines for biologic therapy for psoriasis 2017. *British Journal of Dermatology*, *177*(3), 628–636.

Sneyd, J. R. (2009). Off-label use of medicines is bad medicine flying the flag of clinical freedom. *International Journal of Obstetric Anesthesia*, *18*(3), 249–250.

Sostegni, R. (2003). Crohn’s disease: monitoring disease activity. *Alimentary Pharmacology and Therapeutics*, *17*(s2), 11–17.

Srivastava, S., *et al.* (2010). Beating Heart Totally Endoscopic Coronary Artery Bypass. *Annals of Thoracic Surgery*, *89*(6), 1873–1880.

Strik, A. S., *et al*. (2018). Serum concentrations after switching from originator infliximab to the biosimilar CT-P13 in patients with quiescent inflammatory bowel disease (SECURE): an open-label, multicentre, phase 4 non-inferiority trial. *The Lancet Gastroenterology and Hepatology*, *3*(6), 404–412.

Strober, B. E., *et al.* (2016). Comparative effectiveness of biologic agents for the treatment of psoriasis in a real-world setting: Results from a large, prospective, observational study (Psoriasis Longitudinal Assessment and Registry [PSOLAR]). *Journal of the American Academy of Dermatology*, *74*(5), 851-61.e4.

Stuart Horner, J. (2000). Autonomy in the medical profession in the United Kingdom - An historical perspective. *Theoretical Medicine and Bioethics*, Vol. 21, pp. 409–423.

Tada, Y., *et al.* (2019). Patient preference for biologic treatments of psoriasis in Japan. *The Journal of Dermatology*, *46*(6), 466–477.

Tarallo, M., *et al.* (2019). Costs associated with non-medical switching from originator to biosimilar etanercept in patients with rheumatoid arthritis in the UK. *Journal of Medical Economics*, *22*(11), 1162–1170.

Tyssen, R., *et al.* (2013). Physicians’ perceptions of quality of care, professional autonomy, and job satisfaction in Canada, Norway, and the United States. *BMC Health Services Research*, *13*(1), 516.

Vasconcellos, J. B. *et al.* (2016). Paradoxical psoriasis after the use of anti-TNF in a patient with rheumatoid arthritis. *Anais Brasileiros de Dermatologia*, *91*(5 suppl 1), 137–139.

Warwicker, T. (1998). Managerialism and the British GP: the GP as manager and as managed. *International Journal of Public Sector Management*, *11* (2/3), 201–221.

Williams, A. (1988). Health economics: the end of clinical freedom? *BMJ*, *297*(6657), 1183–1186.

Wong, U., & Cross, R. K. (2019). Expert opinion on interleukin-12/23 and interleukin-23 antagonists as potential therapeutic options for the treatment of inflammatory bowel disease. *Expert Opinion on Investigational Drugs*, *28*(5), 473–479.

Yanai, H., *et al.* (2015). Levels of drug and antidrug antibodies are associated with outcome of interventions after loss of response to infliximab or adalimumab. *Clinical Gastroenterology and Hepatology : The Official Clinical Practice Journal of the American Gastroenterological Association*, *13*(3), 522-530.e2.

Yau, Y. Y., *et al.* (2017). Serological Epithelial Component Proteins Identify Intestinal Complications in Crohn’s Disease. *Molecular & Cellular Proteomics : MCP*, *16*(7), 1244–1257.

Young, A. P. (1997). Competing Ideologies in Health Care: a personal perspective. *Nursing Ethics*, *4*(3), 191–201.

Young, D. W. (1982). A survey of decision aids for clinicians. *British Medical Journal*, *285*(6351), 1332–1336.

Zeebregts, C. J., *et al.* (2003). Synchronous tumours of the unilateral parotid gland: Rare or undetected? *Journal of Cranio-Maxillofacial Surgery*, *31*(1), 62–66.