Search type

Pubmed: (("randomized controlled trial"[pt] OR "controlled clinical trial"[pt] OR randomized[tiab] OR placebo[tiab] OR "drug therapy"[sh] OR randomly[tiab] OR trial[tiab] OR groups[tiab]) AND (("Drug Monitoring"[Mesh]) OR ((((Monitoring, Drug[Title/Abstract]) OR (Therapeutic Drug Monitoring[Title/Abstract])) OR (Drug Monitoring, Therapeutic[Title/Abstract])) OR (Monitoring, Therapeutic Drug[Title/Abstract])))) AND (("Colitis, Ulcerative"[Mesh]) OR ((((Idiopathic Proctocolitis[Title/Abstract]) OR (Ulcerative Colitis[Title/Abstract])) OR (Colitis Gravis[Title/Abstract])) OR (Inflammatory Bowel Disease, Ulcerative Colitis Type[Title/Abstract])))

Cochrane: (("randomized controlled trial"[pt] OR "controlled clinical trial"[pt] OR randomized[tiab] OR placebo[tiab] OR "drug therapy"[sh] OR randomly[tiab] OR trial[tiab] OR groups[tiab]) AND (("Drug Monitoring"[Mesh]) OR ((((Monitoring, Drug[Title/Abstract]) OR (Therapeutic Drug Monitoring[Title/Abstract])) OR (Drug Monitoring, Therapeutic[Title/Abstract])) OR (Monitoring, Therapeutic Drug[Title/Abstract])))) AND (("Colitis, Ulcerative"[Mesh]) OR ((((Idiopathic Proctocolitis[Title/Abstract]) OR (Ulcerative Colitis[Title/Abstract])) OR (Colitis Gravis[Title/Abstract])) OR (Inflammatory Bowel Disease, Ulcerative Colitis Type[Title/Abstract])))

Embase: (‘ulcerative colitis'/exp OR ‘chronic ulcerative colitis':ab,ti OR ‘colitis ulcerativa':ab,ti OR ‘colitis ulcerosa':ab,ti OR ‘colitis ulcerosa chronica':ab,ti OR ‘colitis, mucosal':ab,ti OR ‘colitis, ulcerative':ab,ti OR ‘colitis, ulcerous':ab,ti OR ‘colon, chronic ulceration':ab,ti OR ‘histiocytic ulcerative colitis':ab,ti OR ‘mucosal colitis':ab,ti OR ‘ulcerative colorectitis':ab,ti OR ‘ulcerative procto colitis':ab,ti OR ‘ulcerative proctocolitis':ab,ti OR ‘ulcerous colitis':ab,ti) AND (‘Drug Monitoring'/exp OR ‘medication monitoring':ab,ti OR ‘monitoring, drug':ab,ti OR ‘therapeutic drug monitoring':ab,ti)

Supplementary Table 1 Study characteristics

Author, year Paper/abstract	Country,study type and comparison	Single or multicentre Design N	Population[1]	Intervention	Optimization algorithm	Comparator	Outcomes	Follow-up duration
Vande Casteele N(2015), paper[1]	Belgium, RCT,Proactive vs empiric	Single-centre RCT 263(178 CD and 85 UC)	IFX maintenance therapy in adult, moderate to severeUC, IFX responders	Proactive TDM, ELISA before each injection	3-7 g/mL: No change; > 7 g/mL: 1) at a dose of up to 5mg / kg, and 2) at an interval of 2 weeks (maximum q12 weeks); <3 g/mL: 1) at 2 weeks apart (minimum q4 weeks), and 2) at a dose up to 10mg / kg	Empirric IFX optimization based on symptoms and CRP	Prim: Clinical (HBI 4 or PMS 2 no score> 1) and biochemical (CRP 5 mg/L) remission for 1 year	1 year 53 months in follow-up study

Random optimizati on up to 3-7 g / mL after IFX TC		sec: durable remission, relapse (requiring anti-TNF upgrade, steroid or treatment change), ADAb, cost, QALY, IFX failure, safety Subsequent studies of IFX persistence and immunogenic

							ity	
Sánchez-Hernández JG(2020),paper[2]	Spain,Observational, Proactive vs empiric	Single-center prospective cohort study 81 Retrospective control group 72 N- =148 (84 CD, 64 UC, 12 children)	Patients with moderate or severe UC	Proactive TDM, week 14 determined the first TSIC (trough concentration) of ELISA	Treatment at week 12 and at week 14 was 5-10 gmL 1,Maintenance period of 3-10 gmL 1.Concentrations greater than 10 gmL 1 were used in patients with CD and perianal ostomy.A total of 23 ATIs were tested in patients with TSIC <1 gmL 1	Receive the empirical administration of drug therapy	Dose adjustment according to standard of care showed that 48.1% of the patients had subtherapeutic tsic and 13.5% had ATIs. Early active TDM: Mep-TDM was	3years

							performed in 81 patients who were started with infliximab, and a total of 201 tsic was measured over 3 years.	
Bernardo S(2017), abstract[3]	Portugal,Observational, Proactive vs empiric	Single-center retrospective cohort study N=218 (34UC)	IBD patients receiving IFX (N=210) or ADA (N=8),It is mainly for	Proactive TDM (ELISA), approximately every 6 months	The IFX in the UC is 5-10 g/mL; The ADA in the UC is 7-9 g/mL	Experience anti-TNF optimization	Prim: clinical remission (no hospitalization, surgery or treatment failure / switching) Sec: FC < 50 μ	48weeks

			maintenance therapy				g / ml, seizure, hospitalization, surgery	
Fernandes SR(2020),paper[4]	Portugal,Observational, Proactive vs empiric	A single-center, prospective cohort study Retrospective cohort of the control group N=20,153	The subject was confirmed as having a UC. A total of 13 patients successfully completed IFX induction	Chitch levels and anti-drug antibodies were measured using ELISA	According to the prespecified Valley level interval (uc5-10 μ g / ml), the drug level accounted for 49.0% of the measurement of UC patients (disease P < 0.001). The IFX Valley level was between 3-7ug/ml (CD) and 5-10ug/ml (UC); For patients with trough levels below the	Experience IFX Optimization	Treatment escalation was more common in PTDM patients, with less surgery rate (8.9% vs 20.8%; P = 0.032) and higher mucosal healing rate	2years

		CD, 52 UC, 56 active treatment regimen	therapy (0,2 and 6 weeks) And for patients who meet the inclusion conditions		specified threshold, escalation was achieved by increasing the drug dose (7.5mg/kg or 10mg/kg) or reducing the dosing interval (every 6 or 4 weeks)		(73.2% vs 38.9%; P < 0.0001). Active TDM significantly reduced the odds of adverse outcomes (odds ratio, 0.358; 95% confidence interval, 0.188 – 0.683; P = 0.002).	
Lee H(2019),	United Kingdo	Single-center	Patients were	Proactive TDM	The mean and median of the trough levels of	reactiveness TDM	In the reaction	1.5years

abstract[5]	m,Observational, Proactive vs empiric	retrospective cohort analysis There were 54 patients(UC) 17 cases	within the range of 71 TDM results obtained At least one assay was performed.	infliximab were 3.8mg/ml and 4.7mg/ml (range < 0.4 to > 10mg/ml).	group, 17% (n = 6) changed to substitute biological agents, and in the active group, 7.1% (n = 2) changed to substitute biological agents.The requirements of intestinal surgery in the reactive group and

								the active group were 5.7% (n = 2) and 7.1% (n = 2), respectively.The response group was 8.5% (n = 3) and the biological treatment was stopped, and the active group was zero	
Papamic	USA,	Multi-cen	Maintenan	Proactive	The titers ranged from	Reactive	Adalimumab	The	

hael K(2019), paper[6]	Observational, Proactive vs empiric, Proactive vs reactive	ter retrospective The cohort studied N382 patients with IBD with UC68 and received at least one active TDM [n=53] or standard	ce treatment phase Adalimumab-treated adult patients with IBD	TDM	1.7-> 55U / ml	TDM orEmpirical dose increase	treatment was changed based on the first TDM, 27 / 50 [54%] of patients receiving reactive TDM alone (drug withdrawal, n=14 [ATA, n=5]; treatment escalation, n=13)]	median follow-up period was 3.1 years

		therapy [empirical dose escalation, n=279; reactive TDM, n=50]				
Capoulas M(2020), paper[7]	Portugal,Observational, Proactive vs empiric	Single-center, retrospective, observational study N40,CD36,UC4	adalimumab Maintenance therapy in adult patients with IBD	Proactive TDM	Empirical dose increase	25.1weeks

Papamichael K(2017), paper[8]	USA, Observational, Proactive vs reactive	Multicenter retrospective cohort study N=264(167CD,90UC,7IBD-U）	Adult IBD, the primary IFX responder	Active TDM (+ / -Reactivity), ELISA and HMSA	objective TC5-10μg/mL	reactiveness TDM,Under LOR or infusion reactions	prim: Treatment failure (IFX withdrawal due to LOR or serious adverse event, or surgery) sec: surgery, hospitalization, severe infusion reaction, ADAb	Median value of 2.4 years （IQR1.5-3.3）
Guidi L(2018),	Italy, Observ	Multi-center	In IBD patients,	Reactive TDM	The algorithm was modified from Steanholt	Experience IFX	Prim: Clinical response	12 weeks

paper[9]	ational, Proactive vs empiric	prospective cohort study, retrospective control group N-=148 (84 CD, 64 UC)	IFX was maintained for 4 months with per-second LOR	(ELISA), as described in the LOR	2014, However, using the TC cutoff was 3 g/mL	Optimization	(PMS 2, Rectal bleeding 30% + score 1, HBI 3, plus CRP or FC), Apply TDM to save savings Se: Number of dose increases	
Kelly OB(2017),paper[10]	Canada,Observational, Proactive vs	Single-center retrospective cohort study of	Adult IBD patients who receive IFX maintenan	Reactive TDM, at LOR, HMSA	The interval was reduced by 2 weeks or the dose was increased by 2.5mg / kg	Experience IFX Optimization	Prim: endoscopic remission (MCES ≤1, SES-CD <3 or	Endoscopy and clinical activity were

empiric	N=271 (179 CD, 118 UC, 15 IBD-U)	ce within 3 months of IFX optimization	Rutgeerts ≤i1) Sec: endoscopic improvement (↓ in MCES ≥1, SES-CD >2 or Rutgeerts ≥1), clinical remission (PMS <3, HBI <4 or per physician), clinical response (per physician), hospitalizatio	median 6 months and surgery 12 months

							n, flares, steroid use, IFX persistence, ADAb	
Bossuyt P(2022), paper[11]	Belgium, RCT Pro	Double-centre RCT 187(115 POCT and 72 reactive TDM)	All patients were clinically assessed at each visit and standard laboratory tests (haematol	POCT and reactive TDM, ELISA before each injection	TL measurement of infliximab at inclusion. The value of this measurement determined the follow-up pathway. If the TL was between 3–7 µg/mL, the patient continued infliximab at same dose and interval. If the TL was above 7	All patients were clinically assessed at each visit and standard laboratory tests (haematology, ionogram,	primary endpoint of the study was the percentage of patients with infliximab failure after 1 year , defined as: infliximab discontinuati	1 year

ogy, ionogram, liver test, renal function, C-reactive protein [CRP], albumin) were performed approximately every 12–16 weeks according to	µg/mL, an interval prolongation was allowed but was not compulsory [maximum interval q12 weeks]. If the TL was below 3 µg/mL, the interval was shortened by 2 weeks to a minimum interval of q4 weeks, and subsequent TL measurement was based on a POCT. If this POCT before the administration of infliximab showed an infliximab TL <3 µg/mL,	liver test, renal function, C-reactive protein [CRP], albumin) were performed approximately every 12–16 weeks according to standard of care.	on, IBD-related surgery, IBD-related hospitalisation, add-on IBD treatment, and allergic reaction to infliximab.

standard of care. In this maintenance setting, endoscopy was not routinely performed and faecal calprotectin measurement was performed two times per year	the dose was optimised ad hoc. For the dose optimisation we used a linear dosing formula (Dosen = [TL target * Dose n-1] / TL measured) in order to reach a target TL of 3 µg/ml.

			maximum in patients with CD,					
D'Haens GR(2022),paper[12]	19 Countries; RCT Pro; HIR vs. SIR	multi-center RCT; 514(308 HIR and 206 SIR)	eligible patients were randomized (3:2, stratified by baseline high-sensitivity C-reactive protein [hs-CRP levels <10 mg/L	Proactive TDM	For HIR, patients received adalimumab 160 mg at baseline, and at week 1, week 2, and week 3. For SIR, patients received adalimumab 160 mg at baseline, placebo (adalimumab vehicle) at week 1, adalimumab 80 mg at week 2, and placebo at week 3. Starting at week 4, patients in both groups received	Eligible patients were randomized (3:2, stratified by baseline high-sensitivity C-reactive protein [hs-CRP levels <10 mg/L or ?10	The coprimary end points were the proportions of patients who achieved clinical remission (CDAI score <150) at week 4 and endoscopic response	3years

or ?10 mg/L], prior infliximab use, and CD activity [CDAI score -300 or >300])	adalimumab 40 mg eow through week 12. Concomitant medication use remained stable, except for corticosteroids, for which patients were required to taper their dose starting at week 4 per the protocol-defined taper schedule	mg/L], prior infliximab use, and CD activity [CDAI score ?300 or >300]) to receive adalimumab	(>50% decrease from baseline in SES-CD [or a ?2-point reduction in patients with a baseline SES-CD of 4]) at week 12. All endoscopic assessments were confirmed by a central reader.

Panés J(2022),paper[13]	20 Countries, RCT Pro HIR vs. SIR	Multi-centre RCT 952(573 HIR vs. 379 SIR)	Eligible patients (18–75 years, full Mayo score 6–12, centrally read endoscopy subscore 2–3)	Proactive TDM	Higher induction regimen (adalimumab 160 mg at weeks 0, 1, 2, and 3) or standard induction regimen (160 mg at week 0 and 80 mg at week 2); all received 40 mg at weeks 4 and 6. At week 8, all patients were rerandomized 2:2:1 (main study) to 40 mg every week (ew), 40 mg every other week (eow), or exploratory therapeutic drug monitoring; or 1:1	Adalimumab 40 mg ew maintenance regimen, adalimumab 40 mg eow maintenance regimen, or a TDM	Changes from baseline in IBDQ total score16 were assessed at weeks 2, 4, and 8 (induction study) and weeks 12, 24, 37, and 52 (maintenance study). Changes from baseline in Work Productivity	48weeks

	(Japan substudy) to 40 mg ew or 40 mg eow maintenance regimens.	and Impairment Questionnaire17 and 36-Item Short Form Health Survey18,19 scores were assessed at week 8 (induction study) and week 52 (maintenance study).

[1]IBD denotes a mixed CD and UC population unless otherwise specified.

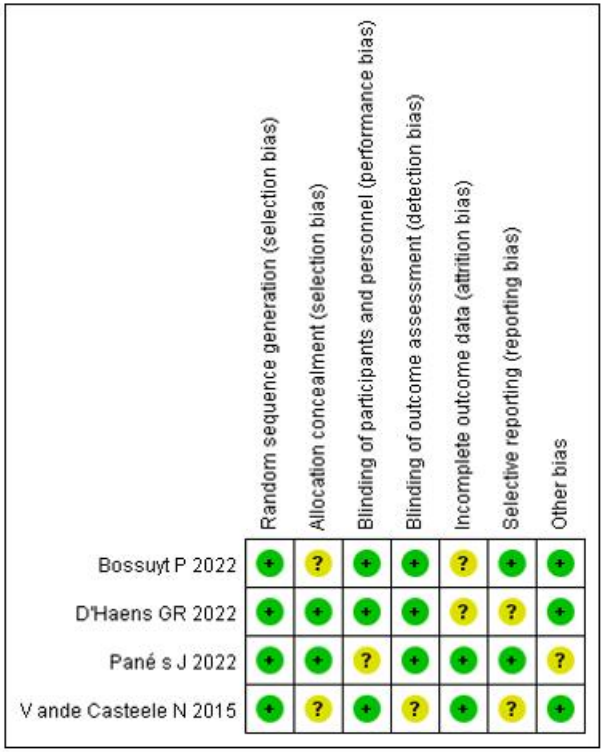
Prim-primary; Sec-secondary; ADAb-anti-drug antibodies; CDAI-Crohn's disease activity index; CDEIS-Crohn's disease endoscopic index of severity; CRP- C-reactive protein; ECLIA-electrochemoluminescence assay; ELISA-enzyme-linked immunosorbent assay; FC-fecal calprotectin; HBI-Harvey-Bradshaw Index; HMSA-homogeneous shift assay; IBD-inflammatory bowel disease; IBDQ-IBD questionnaire; IFX-infliximab; LOR-loss of response; MCES-Mayo Clinic endoscopic subscore; MH-mucosal healing; MTX-methotrexate; PDAI-perianal disease activity index; PMS-partial Mayo score; QALY-quality adjusted life year; SES-CD-simple endoscopic score for Crohn disease; TC-trough concentration.

Supplementary Table 2 Summary of NOS score

Publication (yr)	Representativeness of the exposed cohort	Selection of non-exposed cohorts	Exposure determination	None of the subjects had developed the disease under study at the start of the study	Comparability of exposed and non-exposed cohorts (design and analysis phase)	Result determination method	Is the follow-up period long enough for the disease under study?	Completeness of follow-up	Overall rating and TOTAL SCORE/10
Sánchez-Hernández JG(2020),paper [2]	1	1	1	0	1	1	1	1	7
Bernardo S(2017),abstra	1	0	1	0	1	1	1	1	6

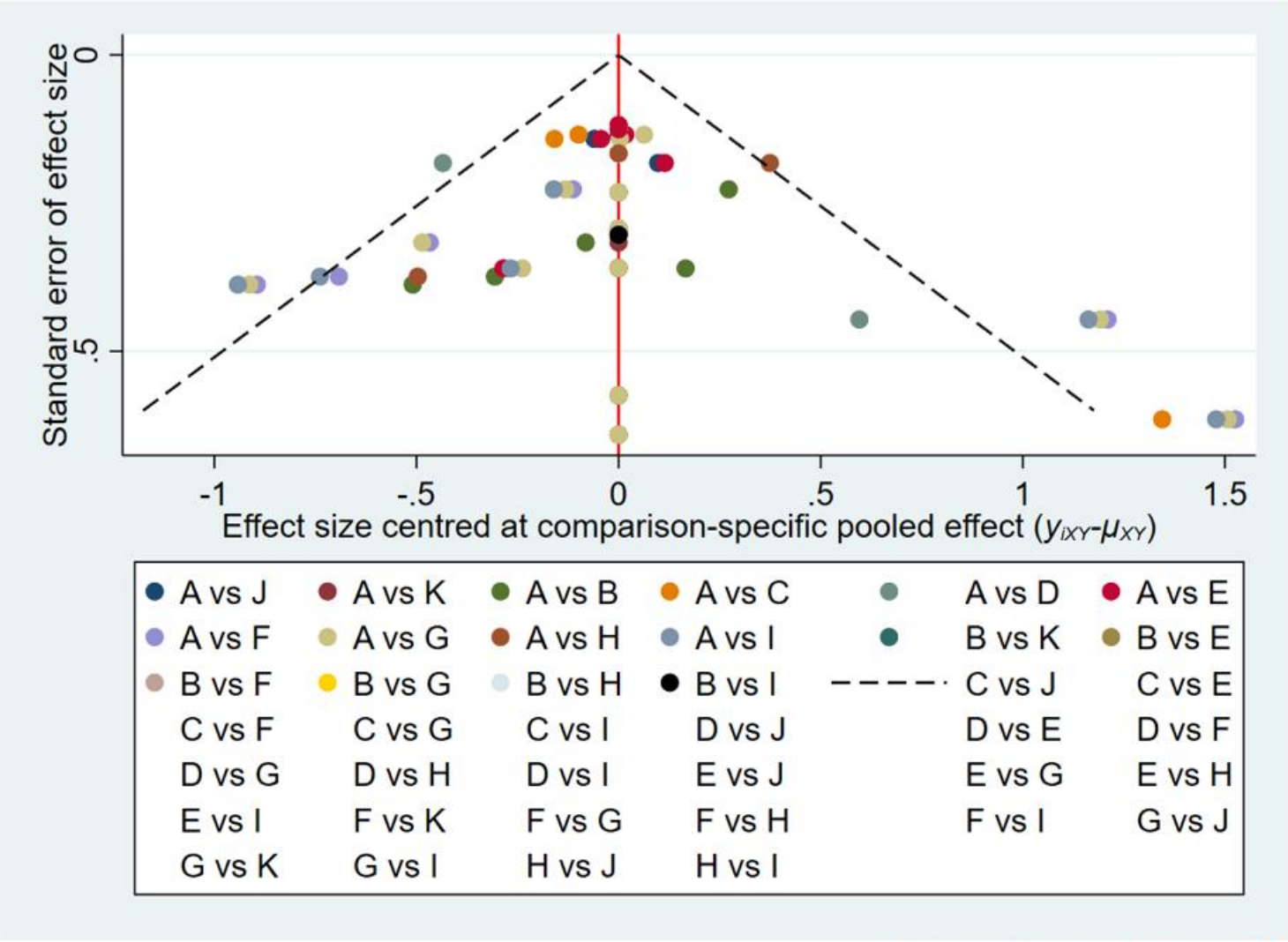
ct[3]									
Fernandes SR(2020),paper[4]	1	1	1	0	1	1	1	1	7
Lee H(2019), abstract[5]	1	1	1	0	1	1	1	1	7
Papamichael K(2019),paper[6]	1	1	1	0	2	1	1	1	8
Capoulas M(2020),paper[7]	1	1	1	0	1	1	1	1	7
Papamichael K(2017),paper[8]	1	1	1	0	1	1	1	1	7
Guidi L(2018),paper[9]	1	1	1	0	2	1	1	1	8
Kelly OB(2017),pape	1	1	1	0	1	1	1	1	7

r[10]



DOI: 10.4240 /wjgs.v0.i0.0000

Supplementary Figure 1 Summary of risk of bias.



DOI: 10.4240 /wjgs.v0.i0.0000

Supplementary Figure 2 Network funnel plot of of proactive therapeutic drug monitoring versus conventional management efficacy in clinical remission outcome.