

Table S1. Rome IV criteria: irritable bowel syndrome

Diagnostic time frame	Symptom description	Symptoms
① ≥ 3 months of persistent symptoms with symptom onset at least 6 months before diagnosis	Abdominal pain	Recurrent association (2 or more) of the following criteria: ① Related to defecation ② Associated with a change in the form of stool ③ Associated with a change in the frequency of stool
② ≥ 1 day per week		
IBS-D	$\geq 25\%$ of bowel movements of Bristol stool form types 6 or 7, and $< 25\%$ of Bristol stool form types 1 or 2.	
IBS-C	$\geq 25\%$ of bowel movements of Bristol stool form types 1 or 2, and $< 25\%$ of Bristol stool form types 6 or 7.	
IBS-M	$\geq 25\%$ of bowel movements of Bristol stool form types 1 or 2, and $\geq 25\%$ of bowel movements of Bristol stool form types 6 or 7.	

NOTE: IBS-C, IBS with constipation; IBS-D, IBS with diarrhoea; IBS-M, IBS with mixed bowel habits.

Table S2. Refractory irritable bowel syndrome (IBS)

Items

1. IBS according to the Rome IV criteria;
 2. Symptoms are present for ≥ 12 months;
 3. Absence of response to an adequate dose of at least one conventional pharmacological agent tried for a minimum of 6 weeks;
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NOTE: IBS, irritable bowel syndrome.

Table S3. Locations of acupoints in the acupuncture group

Acupoints		Locations
Tianshu (ST25)	Bilateral	On the same level of the umbilicus, and 2 cun ^a lateral to the anterior midline
Shangjuxu (ST37)	Bilateral	6 cun directly below Dabi (ST35), and one finger-breadth lateral to the anterior border of the tibia
Zusanli (ST36)	Bilateral	3 cun directly below Dabi (ST35), and one finger-breadth lateral to the anterior border of the tibia
Neiguan (PC6)	Bilateral	On the line joining Daling (PC7) and Quze (PC3), between the tendons of palmaris longus and flexor carpi radialis, 2 cun above the transverse crease of the wrist

^a 1 cun (≈20 mm) is defined as the width of the interphalangeal joint of patient's thumb

Table S4. Locations of non-acupoints in the sham acupuncture group

Non-acupoints		Locations
Non-acupoint 1	Bilateral	In the middle of Daheng (SP15) and Zhangmen (LR13) points (lateral aspect)
Non-acupoint 2	Bilateral	In the medial arm on the anterior border of the insertion of the deltoid muscle at the junction of the deltoid and biceps muscles
Non-acupoint 3	Bilateral	On the same level 1-2 cun ^a outboard lateral of the ST36
Non-acupoint 4	Bilateral	In the middle of the medial epicondyle of the humerus and the styloid process of ulna

^a 1 cun (≈ 20 mm) is defined as the width of the interphalangeal joint of patient's thumb

Table S5. Adherence of total acupuncture sessions

Group	Poor adherence, <i>n</i>^a	Good adherence, <i>n</i>	Total	<i>P</i>
Acupuncture Group	7	78	85	0.79
Sham Acupuncture Group	8	77	85	

NOTE: adherence=actual sessions of treatment/total 12 sessions.

^a Patients who completed less than 80% of the treatment protocol.

Table S6. The types of IBS pharmacological treatments newly added during the 4-week treatment

Treatment course of newly added interventions		Acupuncture Group (<i>n</i> = 85)		Sham Acupuncture Group (<i>n</i> = 85)		Total N	P
		n1	%	n2	%		
No added medication	NA	80	95%	76	89%	156	0.26
Unclear	Chinese herbal medicine	1	1%	1	1%	2	> 0.99
	Probiotics-Spasmolytic	1	1%	0	0	1	—
	Chinese herbal medicine	1	1%	3	4%	4	0.25
≤7 sessions	Anti-diarrheal agents	0	0	1	1%	1	—
	Neurotransmitter pharmaceutical	1	1%	0	0	1	—
	Others ^a	0	0	3	4%	3	—
8-14 sessions	Chinese herbal medicine	1	1%	1	1%	2	> 0.99

NOTE: NA=not applicable.

^a Others include health care medicine, and medication outside the guidelines.

Table S7. Patients who continued treatment as usual (TAU) and medications during four weeks' treatment

Variable	Acupuncture + TAU medications		Acupuncture + TAU		Acupuncture Group	
	n	Mean (95% CI)	n	Mean (95% CI)	N	Mean (95% CI) ^a
Change of the total IBS-SSS from baseline at week 4	23	135.3 (95.5 to 175.2)	62	146.7 (127.7 to 165.6)	85	140.0 (126.0 to 153.9)
	Sham Acupuncture + TAU medications		Sham Acupuncture + TAU		Sham Acupuncture Group	
	n	Mean (95% CI)	n	Mean (95% CI)	N	Mean (95% CI) ^a
	15	106.9 (51.9 to 161.9)	70	50.8 (36.0 to 65.6)	85	64.4 (50.4 to 78.3)

NOTE: IBS-SSS, IBS Symptom Severity Score; TAU, treatment as usual.

^a The primary outcome was analyzed with analysis of covariates and adjusted for baseline total IBS-SSS.

Table S8. The differences in relative changes between the two groups of primary outcome

Variable	Acupuncture Group (n = 85)	Sham Acupuncture Group (n = 85)	Difference (95% CI)	P
Primary outcome				
Change from baseline in total IBS-SSS at week 4 (relative changes in reduced values), %	55.6 (48.8.4 to 62.4)	20.4 (13.5 to 27.2)	35.2 (25.6 to 44.9)	< 0.001

NOTE: IBS, irritable bowel syndrome; IBS-SSS, IBS Symptom Severity Score.

Table S9. Mixed-effect model results on reduction in the total IBS-SSS

Variable	Acupuncture Group (<i>n</i> = 85)	Sham Acupuncture Group (<i>n</i> = 85)	Difference (95% CI)	<i>P</i>
Change of the total IBS-SSS from baseline, adjusted mean (95% CI) ^a				
Week 4	135.5 (108.8 to 162.2)	81.1 (58.6 to 103.5)	54.5 (19.6 to 89.3)	.002
Week 8	130.8 (100.2 to 161.3)	87.3 (61.6 to 112.9)	43.5 (3.6 to 83.4)	0.03

NOTE: IBS-SSS, Irritable Bowel Syndrome Symptom Severity Score. Score range 0-500 (best score 0).

^aThe change from baseline in the total IBS-SSS at weeks 4 and 8 were analyzed by fitting a mixed-effect model using baseline value as a covariate, treatment as a fixed effect, and site as random effects accounting for center differences.

Table S10. Multivariable linear Model on change in the total IBS-SSS score

Variable	Acupuncture Group (n = 85)	Sham Acupuncture Group (n = 85)	Difference (95% CI)/F	P
Change of the total IBS-SSS from baseline, adjusted mean (95% CI) ^a				
Week 4	140.6 (126.4 to 154.9)	63.7 (49.4 to 77.9)	77.0 (56.6 to 97.4)	< .001
Baseline IBS-SSS score	-	-	58.60	< .001
Centre	-	-	0.24	0.63
Age	-	-	0.93	0.34
Gender	-	-	0.77	0.38
BMI	-	-	1.02	0.32
Disease duration	-	-	0.003	0.95
Subtypes	-	-	0.00	> 0.99
Week 8	147.3 (131.7 to 163.0)	85.2 (69.6 to 100.9)	62.1 (39.7 to 84.6)	< .001
Baseline IBS-SSS score	-	-	47.50	< .001
Centre	-	-	0.02	0.90
Age	-	-	1.67	0.20
Gender	-	-	1.06	0.31
BMI	-	-	0.23	0.63
Disease duration	-	-	0.99	0.32
Subtypes	-	-	0.01	0.93

NOTE: IBS-SSS, Irritable Bowel Syndrome Symptom Severity Score. Score range 0-500 (best score 0).

^aThe change from baseline in the total IBS-SSS was analyzed by a multivariable linear model using several baseline factors as covariates, including baseline total IBS-SSS score (when change in the total IBS-SSS from baseline was analyzed, baseline total IBS-SSS was set as a covariate), centre, age, gender, BMI, disease duration, and subtype of IBS. The results were similar to our primary analysis.

Table S11. Subgroup analysis according to IBS subtype on change in the total IBS-SSS at week 4

IBS subtype	<i>n</i>	Acupuncture Group (<i>n</i> = 85)	Sham Acupuncture Group (<i>n</i> = 85)	Difference (95% CI)^a	<i>P</i>
IBS diarrhea ^b	155	144.3 (126.4 to 162.3)	59.5 (42.4 to 76.6)	84.9 (60.2 to 109.5)	< .001
IBS constipation ^c	5	71.5	97.5	NA	-
Mixed IBS ^b	10	146.8 (72.6 to 220.9)	49.2 (-6.6 to 105.1)	97.5 (21.9 to 173.2)	0.02

NOTE: IBS, irritable bowel syndrome. IBS-SSS = Irritable Bowel Syndrome Symptom Severity Score.

^a Differences are mean (95% CI) unless stated otherwise.

^b Continuous variables were reported as mean (95% CI).

^c The sample size for IBS constipation was insufficient (one in acupuncture group and four in sham acupuncture group).

Table S12. Analysis of variance for repeated measurements of IBS-SSS, IBS-QOL, SAS, and SDS in two groups

Variable	<i>W</i>	<i>P</i>	Time effect		Intergroup effect		Interaction effect	
			<i>F</i>	<i>P</i>	<i>F</i>	<i>P</i>	<i>F</i>	<i>P</i>
IBS-Symptom Severity Score ^a	0.73	< 0.05	95.13	< .001	18.75	< .001	13.07	< .001
IBS-Quality of Life score ^a	0.87	< 0.05	41.92	< .001	0.16	0.69	9.28	< .001
Self-Rating Anxiety Scale score	0.97	0.08	31.26	< .001	0.01	0.90	1.81	0.17
Self-Rating Depression Scale score ^a	0.91	0.01	13.06	< .001	0.22	0.64	0.38	0.68

NOTE: IBS, irritable bowel syndrome. IBS-SSS, IBS Symptom Severity Score; IBS-QOL, IBS-Quality of Life; SAS, Self-Rating Anxiety Scale; SDS, Self-Rating Depression Scale.

^aMauchly's sphericity test was performed to determine whether the violation of sphericity occurs, and the multivariate analysis of variance was used when the violation of sphericity occurs.

Table S13. Comparison of total scores of IBS-SSS, IBS-QOL, SAS and SDS at different time points

Variable	Group	Baseline	Week 2	Week 4	Week 6	Week 8
IBS-SSS score	Acupuncture Group (<i>n</i> = 85)	257.6 (70.2)	164.3 (83.3)	113.7 (69.1)	124.4 (87.1)	106.6 (76.8)
	Sham Acupuncture Group (<i>n</i> = 85)	244.7 (71.8)	206.6 (71.9)	183.9 (74.5)	173.8 (86.5)	162.1 (81.7)
	<i>P</i>	0.24	.001	< .001	< .001	< .001
IBS-QOL score	Acupuncture Group (<i>n</i> = 85)	27.3 (17.1)	19.9 (15.5)	14.3 (11.2)	-	-
	Sham Acupuncture Group (<i>n</i> = 85)	23.4 (13.8)	21.6 (13.2)	18.8 (11.0)	-	-
	<i>P</i>	0.11	0.46	0.01	-	-
SAS score	Acupuncture Group (<i>n</i> = 85)	45.7 (10.4)	43.0 (9.3)	40.5 (9.5)	-	-
	Sham Acupuncture Group (<i>n</i> = 85)	44.4 (9.4)	43.3 (9.3)	41.1 (8.5)	-	-
	<i>P</i>	0.39	0.85	0.67	-	-
SDS score	Acupuncture Group (<i>n</i> = 85)	46.3 (11.7)	43.6 (11.2)	42.9 (12.6)	-	-
	Sham Acupuncture Group (<i>n</i> = 85)	45.4 (9.3)	43.4 (9.9)	41.9 (10.9)	-	-
	<i>P</i>	0.59	0.91	0.56	-	-

NOTE: IBS, irritable bowel syndrome. IBS-SSS, IBS Symptom Severity Score; IBS-QOL, IBS-Quality of Life; SAS, Self-Rating Anxiety Scale; SDS, Self-Rating Depression Scale. Continuous variables were reported as mean (SD).

Table S14. Blinding results

Time	Group	Guess, No. (%)			<i>P</i>	Bang's BI (95% CI)
		Acupuncture Group	Sham Acupuncture Group	Unknow		
At the end of first treatment session	Acupuncture Group (<i>n</i> =85)	53 (62)	1 (1)	31 (37)	0.22	-0.61 (-0.50 to -0.72)
	Sham Acupuncture Group (<i>n</i> =85)	42 (49)	3 (4)	40 (47)		0.46 (0.34 to 0.58)
At the end of 12th treatment session ^a	Acupuncture Group (<i>n</i> =81)	70 (86)	0 (0)	11 (14)	< 0.001	-0.86 (-0.79 to -0.94)
	Sham Acupuncture Group (<i>n</i> =80)	37 (46)	4 (5)	39 (49)		0.41 (0.29 to 0.54)

^a For this categorical variable, missing data were not imputed, and the observed data were used in the analysis.

Table S15. Adverse events

Adverse Events ^a	Acupuncture Group (<i>n</i> = 85)		Sham Acupuncture Group (<i>n</i> = 85)	
	Participants, No. (%)	Events, <i>n</i>	Participants, No. (%)	Events, <i>n</i>
Acupuncture-related adverse events				
Severe adverse events	0	0	0	0
Moderate adverse events	0	0	0	0
Mild adverse events	9 (11)	10	4 (5)	5
Skin and subcutaneous tissue				
Subcutaneous hematoma	8 (9)	9	4 (5)	5
Sharp pain	1 (1)	1	0	0
Acupuncture-unrelated adverse events				
Severe adverse events	0	0	0	0
Other				
Cold	1 (1)	1	0	0

^a Adverse events were analyzed in all participants who received randomization.

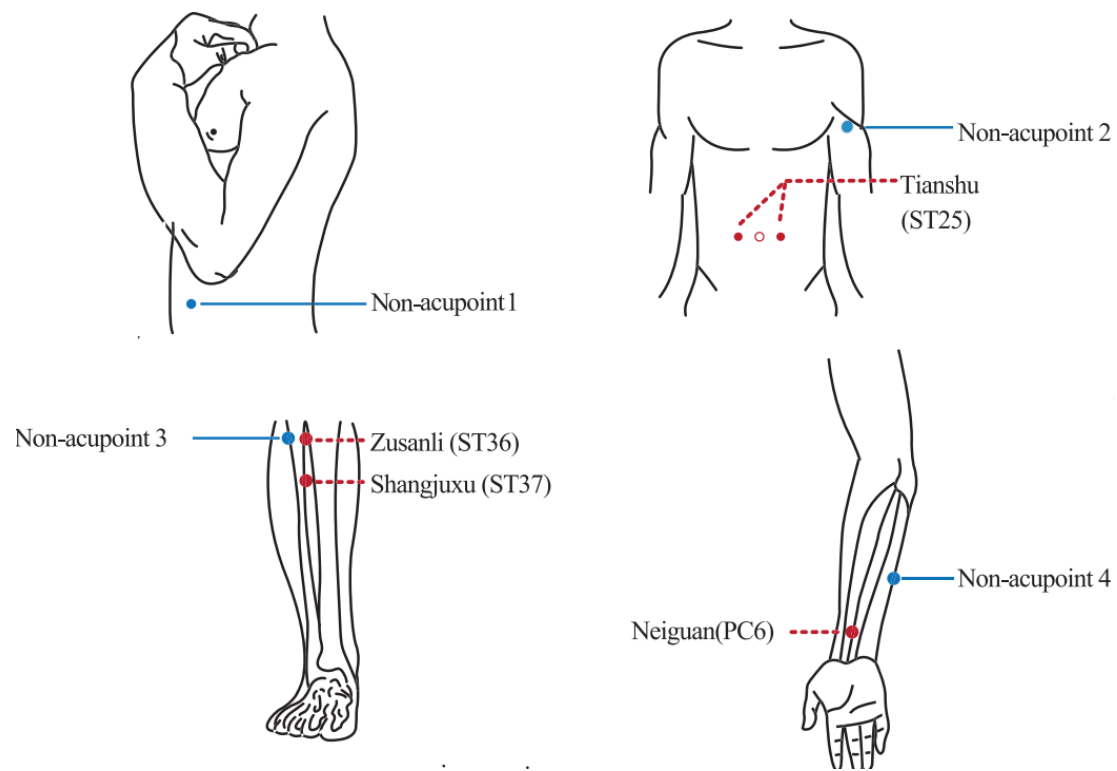


Fig. S1. Location of acupoints and nonacupoints

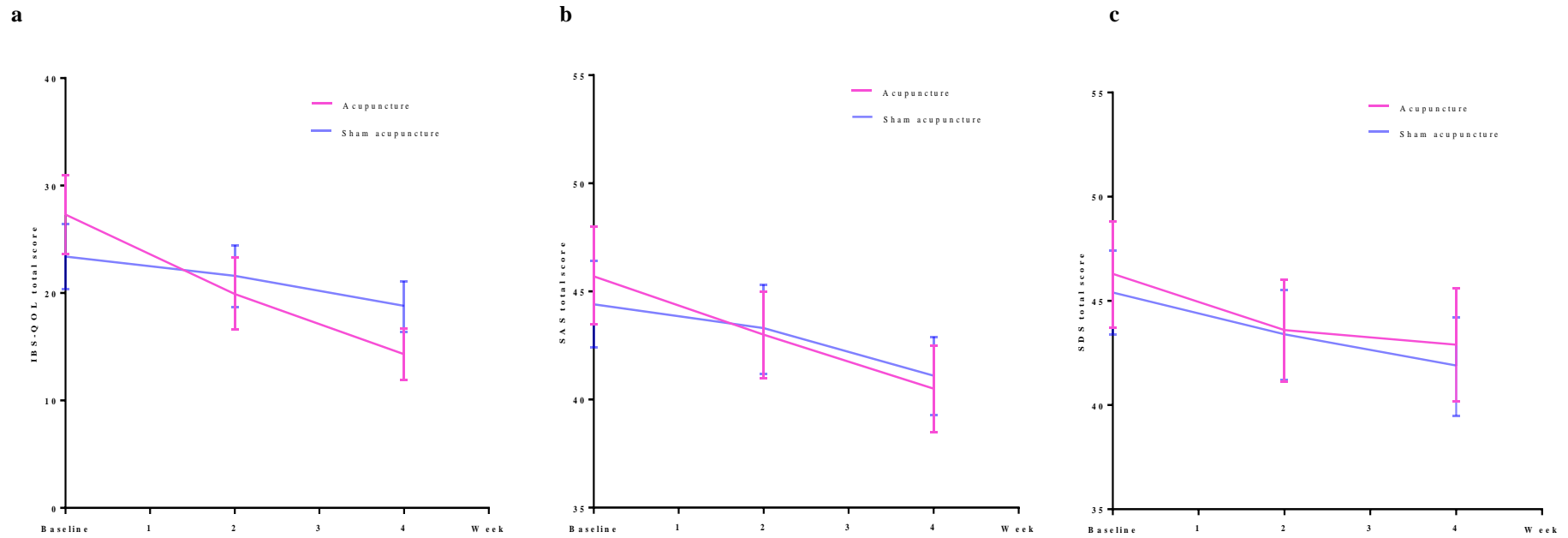


Fig. S2. Schematic diagram of changes in IBS-QOL, SAS and SDS during treatment. IBS, irritable bowel syndrome; IBS-QOL, IBS-Quality of Life; SAS, Self-Rating Anxiety Scale; SDS, Self-Rating Depression Scale

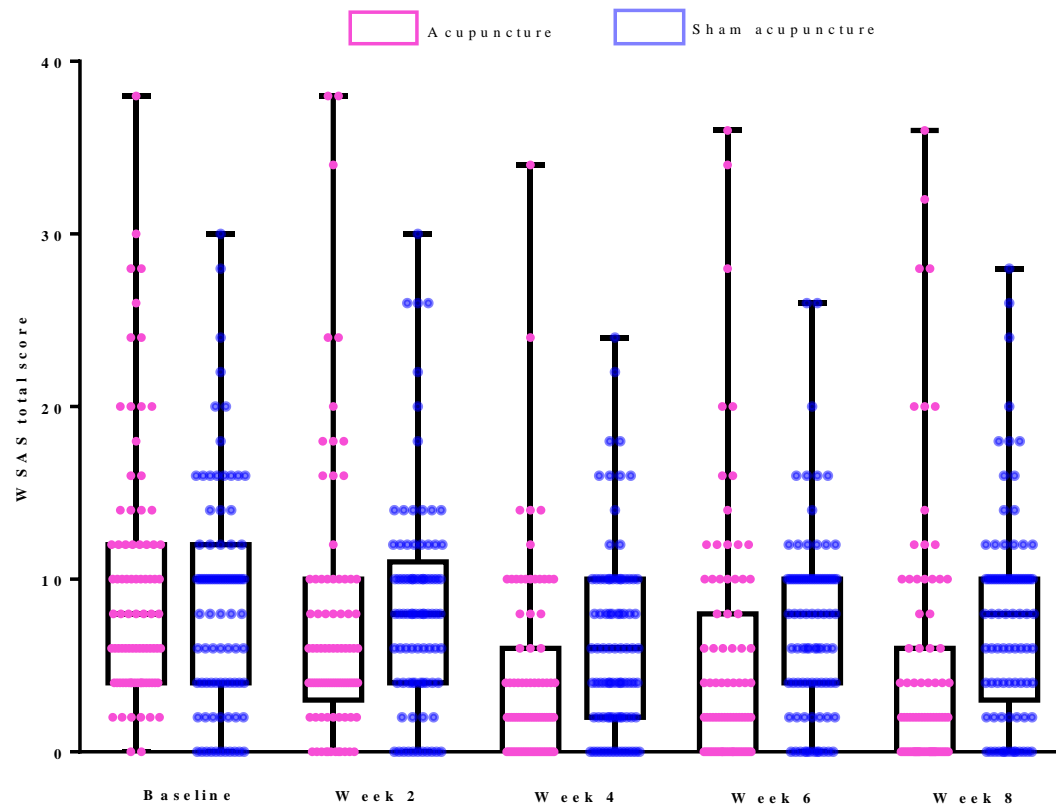


Fig. S3. Schematic diagram of changes in work and social adjustment scale during treatment and follow-up

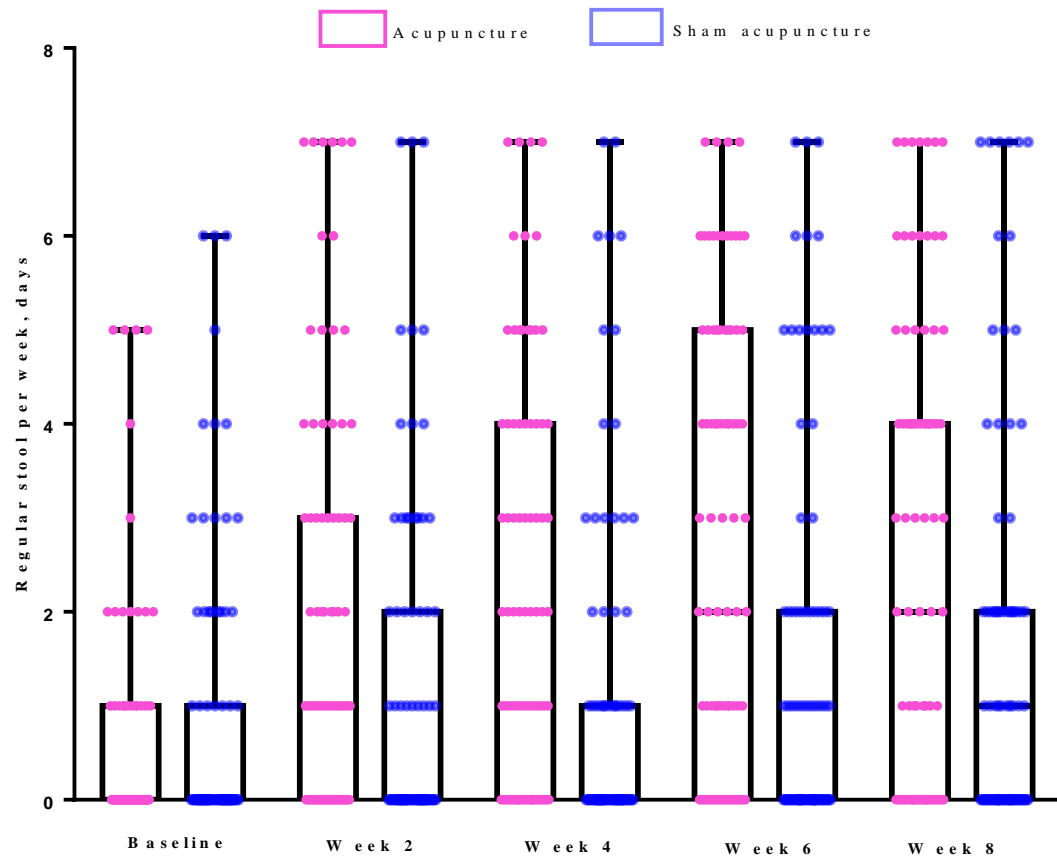


Fig. S4. Schematic diagram of changes in regular stool per week during treatment and follow-up