Supplementary Materials: The Current Status of Clinical Research Involving Microneedles: A Systematic Review

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Table S1. Grade of adverse event by Common Terminology Criteria for Adverse Events (CTCAE).

Grades	Clinical Descriptions
Grade 1	Mild : asymptomatic or mild symptoms; intervention not indicated
Grade 2	Moderate : minimal, local or noninvasive intervention indicated
Grade 3	Severe but not immediately life-threatening : hospitalization indicated
Grade 4	Life-threatening consequences : urgent intervention indicated
Grade 5	Death related to adverse event

This criteria is a modification of the Common Terminology Criteria for Adverse Events (CTCAE, Version 5.0) of department of health and human services (US).

Table S2. Analysis of outcomes in included studies.

Author, Year, Country	Design	Participants Disorder, N (Int./Con.)	Intervention: Type of MNs	Control	Treatment Procedure 1) site of MNs	2) N of Treatment (Duration, Frequency)	Outcome Measure	Results (Based on Between Groups Differences)
					Scar			
Khater, 2016, Egypt [1]	CCT	Striae distensae, 20(10/10)	MTS	CO2 laser	Int: Thighs, legs Con: Abdomen, lower limbs	3 (3-mon, monthly)	[6-mon after final treatment] 1. Physician' assessment (0-4 scale); **2.** Patient satisfaction (0-4 scale); **3.** Biopsy	1,2. $p < 0.001$; **3.** ND
Busch, 2018, Germany [2]	RCT*	Hypertrophic burn scar, 19(19/19)	A. MTS + vitamin, nourishing product	B. No treatment; C. No treatment (healthy skin)	A,B: Scar (randomly) C: Healthy skin	5 (6-12-mon, ND)	[12-mon after final treatment] 1. POSAS ①Observer (thickness, pliability, and surface area) ② Patient (pruritus, thickness, relief, rigidity); 2. Skin moisture (Corneometer); 3. TEWL	1~3. ND
Ryu, 2013, Korea [3]	CCT	Striae distensae, 30(10/10/10)	A. MRF; B. MRF + CO2 laser	C. CO2 laser	Abdomen, hips, or calves	3 (3-mon, monthly)	[6-mon after final treatment] 1. Physician's global assessment (1-4 scale); 2. Patient satisfaction; 3. Biopsy	1~3. ND
Chae, 2015, Korea [4]	RCT	Atrophic acne scar, 40(20/20)	MRF	Er:Glass fractional laser	Face (acne scars)	3 (12-wk, 1/4-wk)	[8-wk after final treatment] 1. Patient satisfaction (1-5 scale); 2. Physician's global assessment (1-5 scale); 3. Scar severity (ECCA grading scale)	1,2. ND; 3. NS
					Facial wrinkle			
Jeon, 2013, Korea [5]	CCT*	Wrinkles, 12(12/12)	MRF	BoNT/A injection	Periorbit (other side per group)	3 (Int) (6-wk, 1/3-wk); 1 (con)	[At 3, 6, 18-wk] 1. Wrinkle grade (0-5 scale); 2. Skin elasticity (Cutometer); 3. Patient satisfaction (1-4 scale)	1. $p < 0.05$ (Int<Con at 3,6-wk; Int>Con at 18-wk); 2. NS; 3. $p < 0.05$ (Int<Con at 3-wk), NS (at 18-wk)
Lu, 2017, China [6]	RCT*	Wrinkles, 13(13/13)	MRF	Superficial dermal insertion	Face (other side per group)	3 (12-wk, 1/4-wk)	[12-mon after final treatment] 1. Clinical assessment (0-5 scale) ①Infraorbital wrinkle ②Nasolabial groove ③Overall improvement	1. ①NS ②$p < 0.05$ (Int<Con) ③ND
Lee, 2016, Korea [7]	CCT*	Wrinkles, 23(23/23)	MAP	Placebo patch	Periorbit (other side per group)	21 (12-wk, 1/4-day)	[At 4, 8, 12-wk] 1. GPS (0-7 scale); 2. Wrinkle seriousness (Visiometer) (R1. Skin roughness, R2. Maximum roughness, R3. Average roughness, R4. Smoothness depth, R5. Arthnetic average roughness)	1. $p < 0.05$ (at 12-wk); 2. $p < 0.05$ (R1, R2, R3 at 12-wk)

Hong, 2018, Korea [8]	RCT	Wrinkles, 84(27/27/30)	A. MAP; B. MAP + wrinkle cream	C. Wrinkle cream	Periorbit and nasolabial fold	3 (12-wk, 1/4-wk)	[At 4, 8, 12-wk] 1. Wrinkle improvement (R_a value) ①Crow's feet wrinkle ②Nasolabial fold; 2. Wrinkle grade (0-4 scale) ①Crow's feet wrinkle ②Nasolabial fold; 3. Skin roughness and wrinkle (Visiometer) (R1. Skin roughness, R2. Maximum roughness, R3. Average roughness, R4. Smoothness depth, R5. Arthnetic average roughness); 4. Skin hydration of eye rim (Cutometer, 0-4 scale); 5. TEWL (Vapometer)	[A vs. C] 1. ①,②NS; 2. ①, ②$p < 0.05$ (at 8-wk); 3. (R1~4. ND) R5. NS; 4,5. ND [B vs. C] 1. ①$p < 0.05$ (at 8-wk) ②NS; 2. ①$p < 0.05$ (at 4,8-wk) ②$p < 0.05$ (at 4-12-wk); 3. (R1~4. ND) R5. NS; 4,5. ND
Skin care								
Kim, 2009, Korea [9]	RCT	Facial skin condition, 24(8/8/8)	A. MTS	B. AHA (7%); C. No treatment	Face	6 (6-wk, weekly)	[At 6-wk] 1. Pore; 2. Large pore; 3. Blackhead; 4. Wrinkles; 5. Small pigmentation (number of 1~5); 6. Area of small pigmentation; 7. Number and area of large pigmentation; 8. Change of skin brightness; 9. Satisfaction (1~8, RSA)	1~9. ND
Choi, 2011, Korea [10]	CCT	Facial skin condition, 14(7/7)	MTS + EGF	Treatment by high frequency + EGF	T, U-Zone of face	6 (6-wk, weekly)	[2-wk after final treatment] 1. Skin oil; 2. Skin keratin; 3. Skin moisture; 4. Pore and wrinkle measurement; 5. Satisfaction (0~4, Aphrodite 3)	1~5. ND
Kim, 2016, Korea [11]	RCT*	Facial hyperpigmentation, 45(A.23/23/B.22/22)	MAP	Placebo patch	Int: face (left) Con: face (right)	A: 18 (8-wk, 1/3-day) B: 14 (8-wk, 1/4-day)	[At 4, 8-wk] 1. The skin depigmentation efficacy ①MI (Mexameter) ②ITA° value (Spectrophotometer) 2. Skin depigmentation (Images)	1. ①A. $p < 0.05$ (at 4,8-wk), B. NS (at 4-wk) $p < 0.05$ (at 8-wk) ②A. NS (at 4-wk) $p < 0.05$ (at 8-wk), B. $p < 0.05$ (at 4-wk) NS (at 8-wk); 2. NS
Park, 2017, Korea [12]	RCT*	Skin brightening, 34(34/34)	MAP	Whitening essence	Cheek (other side per group)	16 (8-wk, 2/weekly)	[At 2, 4, 8-wk] 1. Skin brightness (Chromameter); 2. MI change (Mexameter); 3. Skin whitening survey (0-4 scale)	1. $p < 0.05$ (Int<Con at 4-wk; Int>Con at 8- wk); 2. $p < 0.05$ (at 2,4,8-wk); 3. ND
Alopecia								
Yoo, 2010, Korea [13]	CCT*	Alopecia areata, 8(8/8)	MTS + MAL cream	MAL cream	Int: Scalp (right) Con: Scalp (left)	3 (12-wk, 1/4-wk)	[1-mon after final treatment] 1. Hair regrowth (Photograph); 2. Histopathologic change (Microscopic)	1,2. ND

Bao, 2017, China [14]	RCT	Androgenetic alopecia, 60(20/20/20)	A. AMTS; B. AMTS + minoxidil	C. Minoxidil (topical)	Scalp	12 (24-wk, 1/2-wk)	[At 24-wk] 1. Hair density ①The non-vellus hair ②The vellus hair ③The total hair; 2. Hair thickness (the non-vellus hair); 3. Hair growth ① Investigator assessment (7 point scale) ②Patient assessment (5 point scale); 4. Pain (VAS)	[A vs C] 1. ①NS ②$p < 0.05$ (C>A) ③NS; 2. NS; 3,4. ND [B vs C] 1. ①NS ②$p < 0.05$ ③$p < 0.05$; 2. NS; 3. $p < 0.001$; 4. ND
						Actinic Keratosis		
Petukhova, 2017, USA [15]	RCT*	Actinic keratosis, 32(A.16/B.16)	A. MTS + ALA (10-min) B. MTS + ALA (20-min)	C. Placebo roller	Face (other side per group)	1 (1-mon, 1-day)	[At 1-mon] 1. AKs clearance (Photodynamic); 2. TEWL (Tewameter or Vapometer); 3. Pain (VAS); 4. Pain with blue light (VAS)	[A vs C] 1. NS; 2,3. $p < 0.05$; 4. NS [B vs C] 1. $p < 0.05$; 2,3. $p < 0.05$; 4. NS
Spencer, 2016, USA [16]	RCT*	Actinic keratosis, 20 (20/20)	MTS + ALA	ALA only	Face (other side per group)	1 (4-mon, 1-day)	[At 4-mon] 1. Reduction in AKs; 2. Physician's global assessment (Visia camera image)	1. $p < 0.05$; 2. ND
						Diseases of the skin (others)		
Shin, 2012, Korea [17]	RCT*	Acne, 20(20/20)	MRF	CO2 laser	Face (other side per group)	1~2 (ND, ND)	[3-mon after final treatment] 1. Global improvement scale (0-4 scale); 2. The number of papules and pustules; 3. Satisfaction (0-3 scale); 4. Improvement sebum (Sebumeter); 5. Erythema index and pigmentation (Mexameter); 6. Pain (VAS)	1~4,6. NS; 5. ND
Fatemi Naeini, 2015, Iran [18]	CCT*	Axillary hyperhidrosis, 25(25/25)	MRF	Placebo (standby mode)	Axilla (other side per group)	3 (3-mon, 1/3-wk)	[At 3, 6, 9, 21-wk] 1. HDSS score (1-4 scale); 2. Sweating intensity score (VAS); 3. Patients satisfaction (6 point scale); 4. Histological evaluation	1. $p < 0.01$ (at 6~21-wk); 2. $p < 0.001$ (at 3~21-wk); 3,4. ND
Ryu, 2018, Korea [19]	RCT*	Multiple warts, 42(42/42)	MAP	Cryotherapy	Wart (each lesion per group)	ND (until completely cleared, 1/2-wk)	[At 8, 16-wk] 1. The clearance rate; 2. Duration of treatment; 3. PGA and PaGA (0-5 scale); 4. Pain (VAS)	1. ND; 2,3. NS; 4. $p < 0.0001$
						Vaccine delivery		
Hirobe, 2015, Japan [20]	RCT	Influenza vaccine, 40(20/20)	MAP (a,b,c)	SC (a,b,c)	Upper arm (left)	2 (3-wk, 1/3-wk)	[At 7, 21, 28, 42-days] 1. Immunogenicity (HI assay) in sera ①GMT ②Seroconversion ③Seroprotection ④Increase in GMT ⑤Isotypes titer; 2. Immunogenicity (HI assay) in nasal wash ①	1. ①~④ND ⑤NS; 2,3. ND

							Increases in GMT ② Seroconversion ③Isotypes titer; 3. Counting of IFN-γ-producing cells (ELISPOT assay) (a. A/California/7/2009, b. A/Victoria/210/2009, c. B/Brisbane/60/2008)	
Rouphael, 2017, USA [21]	RCT	Influenza vaccine, 100(A.25/B.25/C.25/D.25)	A. MAP (a,b,c); B. MAP-self (a,b,c)	C. Placebo patch; D. IM (a,b,c)	A,C,D: wrist (non-dominant) B: Deltoid region	1 (1-day, 1-day)	[At 28, 180-days] 1. Immunogenicity (HI assay) ① GMT ②Seroprotection③ Seroconversion; 2. Acceptability (1-5 scale) (a. A/Christchurch/16/2010, b. A/Texas/50/2012, c. B/Massachusetts/2/2012)	[A,B vs C] 1. ①NS ② *p* < 0.01 (a,c, A>C, B>C), NS (b) ③NS; 2. ND [A,B vs D] 1. ①,②NS ③*p* < 0.05 (b. A>D, B>D); 2. *p* < 0.05 (28-day)
Fernando, 2018, Australia [22]	RCT	Influenza vaccine, 60(A.15/B.15/C.15/D.5/E.5/F.5)	A. MAP (FA, a,b,c); B. MAP (UA, a,b,c)	C. IM; D. Placebo MNs (FA, a,b,c); E. Placebo patch (UA, a,b,c); F. Placebo IM	A,D: volar forearm (FA) B,E: upper arm (UA) C,F: Deltoid region	2) 1 (1-day, 1-day)	[At 3, 7, 21, 28-day] 1. Pain (VAS); 2. Acceptability; 3. Immunogenicity (HAI assay) ① GMT ②Seroprotection ③ Seroconversion; 4. Immunogenicity (Microneutralisation assay) ①GMT ②Seroprotection ③Seroconversion (a. A/California/07/2009, b. trivalent Fluvax®)	[A,B vs C] 1,2. ND; 3. NS [A,B vs D,E,F] 1~3. ND
Damme, 2009, Belgium [23]	RCT	Influenza vaccine, 180(A.60/B.60/C.60)	A. Hollow MNs (3µg HA, a,b,c); B. Hollow MNs (6µg HA, a,b,c)	C. IM (15µg HA, a,b,c)	Deltoid region (non-dominant arm)	1 (3-wk, 1-day)	[At 14, 21-day] 1. Pain (VAS) ①Insertion ② Infusion ③Overall; 2. Immunogenicity (HAI assay) ① GMT fold increas ② Seroconversion rate ③ Seroprotection rate (a. A/New Caledonia/20/99, b. A/Wisconsin/67/2005, c. B/Malaysia/2506/2004)	[A vs C] 1. ①,②*p* < 0.05 ③ NS; 2. NS [B vs C] 1. ①*p* < 0.05 ②,③ NS; 2. NS
Laurent, 2010, France [24]	RCT	Rabies vaccine , 66(A.40/B.10/C.14/D.2)	A. Hollow MNs (a,b,c)	B. IM (a,b,c); C. ED (a,b,c); D. Topical (a,b,c)	Deltoid region (non-dominant arm)	3 (21-day, 0,7,21-day)	[At 7, 14, 21, 49-day] 1. Immune response (RFFIT) ① GMT ②Seroconversion rate; 2. Pain (VAS)	[A vs B] 1. NS; 2. A<B (*p* < 0.05) [A vs C,D] 1,2. ND
Frenck, 2011, USA [25]	RCT	Influenza vaccine, 1592(A.400/B.399/C.395/D.	A. Hollow MNs (6µg HA, a,b,c); B. Hollow MNs	C. ID (Mantoux, 3µg HA, a,b,c);	A,B,C: Upper arm; D: Deltoid region	1 (1-day, 1-day)	[At 21-day] 1. Immunogenicity (HAI assay) ① GMT ②Seroconversion rate ③ Seroprotection rate; 2. Pain (VAS)	[A vs C,D] 1,2. ND [B vs C,D] 1,2. ND

		398)	(9µg HA, a,b,c)	D. IM (15µg HA, a,b,c)			(a. A/New Caledonia/20/99 IVR-116, H1N1, b. A/Wyoming/03/2003, H3N2, c. B/Jiangsu/10/2003)	
Levin, 2014, Israel [26]	RCT	Influenza vaccine, 280(A.56/B.56/C.56/D.56/E.56)	A. Hollow MNs (3µg HA, a,b,c)	B. ID (3µg HA, a,b,c); C. ID (4.5µg HA, a,b,c); D. ID (6µg HA, a,b,c)(ID: Mantoux); E. IM (15µg HA, a,b,c)	Deltoid region	1 (1-day, 1-day)	[21-day after final treatment] 1. Immunogenicity (HI assay) ① GMT fold increase ② Seroconversion rate ③ Seroprotection rate (a. A/Solomon Islands/3/2006, b. A/Wisconsin/67/2005, c. B/Malaysia/2506/2004)	[A vs B] 1. ①$p < 0.05$ (a,c) ②$p < 0.05$ (b) ③$p < 0.05$ (c) [A vs C] 1. NS [A vs D] 1. ①$p < 0.05$ (a,c) ②$p < 0.05$ (strain c) ③NS [A vs E] 1. ①$p < 0.05$ (b) ②, ③NS
Anand, 2015, Bangladesh [27]	RCT	Poliovirus vaccine, 922(A.203/B.200/C.156/D.152/E.211)(Type 1~3)	A. Hollow MNs (f-IPV, a,b,c); B. Hollow MNs (f-IPV/bOPV, a,b,c)	C. Oral (tOPV, a,b,c); D. Oral (bOPV, a,c); E. IM (IPV, a,b,c)	Thigh	A,E - 2 (14-wk, 6,14,-wk); B,C,D – 3 (14-wk, 6,10,14-wk)	[At 14, 18, 19-wk] 1. Humoral immunogenicity (CDC) ①Seroconversion by 14-wk ② Seroconversion by 18-wk; 2. Intestinal immunogenicity (CDC): Poliovirus shedding at 19-wk (a. Poliovirus type 1 (PV 1), b. PV 2, c. PV 3)	[A vs C] 1. $p < 0.05$ (①a~c. C>A ②b. A>C); 2. NS [B vs C] 1. $p < 0.05$ (①b,c. C>B); 2. NS [A vs D] 1,2. ND [B vs D] 1. $p < 0.05$ (①a~c. D>B ②b. B>D); 2. $p < 0.05$ (a,c. D>B) [A vs E] 1. ND; 2. NS [B vs E] 1,2. ND
Troy, 2015, USA [28]	RCT	Poliovirus vaccine (HIV patient), 231(A.66/B.66/C.66/D.33)	A. Hollow MNs (IPV: 40% dose, a,b,c); B. Hollow MNs (IPV: 20% dose, a,b,c)	C. IM (IPV: 100% dose, a,b,c) D. IM (IPV: 40% dose, a,b,c)	Deltoid region	1 (1-day, 1-day)	[4~6 wk after final treatment] 1. Polio immunity; ①Baseline ②1 - month after; 2. Vaccine response; 3. Antibody GMT (a. 40D antigen units of serotype 1, b. 8D antigen units of serotype 2, c. 32D antigen units of serotype 3)	[A vs C] 1,2. NS; 3. ND [B vs C] 1. NS; 2. p=0.01 (c), NS (a,b); 3. ND [A,B vs D] 1,2. NS; 3. ND
Levin, 2016, Israel [29]	RCT	Influenza vaccine, 370(A.61/B.61/C.62/D.63/E.63/F.60)	A. Hollow MNs (7.5 µg HA, MJ, a,b,c); B. Hollow MNs (15 µg HA, MJ, a,b,c); C. Hollow MNs (inactivated 15 µg HA,	D. IM (15 µg HA, d); E. IM (45 µg HA, a,b,c); F. IM (15 µg HA with adjuvant, e)	Deltoid region	1 (1-day, 1-day)	[At 22, 90-days] 1. Immunogenicity (HAI assay) ① Seroconversion rate ② Seroprotection rate ③GMT fold increase (a. A/California/7/2009 vaccine, b. A/Victoria/361/2011, c. B/Hubei-Wujiagang/158/2009, d. Inflexal V™, e. Fluad™, f. Intanza™)	[A vs D] 1. Day 22 ①,②$p < 0.05$ (c) ③$p < 0.05$ (b); Day 90 ①$p < 0.05$ (b) ②$p < 0.05$ (c) ③NS [B vs D]1. Day 22 ①$p < 0.05$ (a~c) ②$p < 0.05$ (c) ③$p < 0.05$ (a~c); Day 90 ①$p < 0.05$ (a) ②,③NS [C vs D]1. NS [A,C vs E] 1. NS [B vs E] 1. ①$p < 0.05$ (a at

				SO, f)				day 22) ②,③NS
								[A,B,C vs F] 1. NS
Vescovo, 2017, Switzerland [30]	RCT*	Rabies vaccine, 64(64/64/64)	A.Hollow MNs (a.b)	B. ID (Mantoux, a,b); C. IM (a,b)	A: Left arm; B: Right arm; C: Non-dominant deltoid region	3 (28-day, at 0-, 7-, 28-day)	[At 7, 28, 56-day] 1. Pain (VAS) ①Needle insertion ②Products injection; 2. Immunogenicity (RFFIT) (a. Vaccine, b. Saline)	[A vs B] 1. $p < 0.01$ (①A<B ②a. A<B); 2. NS
								[A vs C] 1. $p < 0.01$ (①A<C ②a. A<C, b. A>C); 2. NS
Insulin delivery								
Pettis, 2011, USA [31]	RCT(cross-over)*	Type 1 diabetes, 29(29/29)	A. Hollow MNs (IL, 2 min premeal inj.) B. Hollow MNs (RHI, 2 min premeal inj.) C. Hollow MNs (RHI, 17 min premeal inj.)	D. SC (IL, 2 min premeal inj.) E. SC (RHI, 17 min premeal inj.)	Periumbilical abdominal wall	5 (ND, washout periods of 3~21-days)	[0~240 min after the meal] 1. PD (Super-GL analyzer); ① Insulin PPG at same time ②From postprandial glycemic excursion; 2. PK (Hodges and Lehmann point) ① INS AUC ②INS$_{max}$ ③tINS$_{max}$; 3. Pain (VAS)	[A vs D] 1. ①NS ②$p < 0.05$ (BG$_{min0-4 h}$); 2. ①$p < 0.05$ (0-0.5,1,1.5,2h) ②,③$p < 0.05$; 3. ND
								[A vs E] 1. ①ND ②NS; 2. NS; 3. ND
								[B vs D] 1. ①NS ②$p < 0.05$ (BG$_{2h}$); 2. ①,②NS ③$p < 0.05$; 3. ND
								[B vs E] 1. ①ND ②NS; 2. NS; 3. ND
								[C vs D] 1. ①ND ②NS; 2. NS; 3. ND
								[C vs E] 1. ①$p < 0.05$ ②$p < 0.05$ (BG AUC$_{0-4h}$, BG$_{0-2h}$, BG$_{max,0-4h}$, BG$_{min,0-2h}$, [BG$_{max}$ $-$ BG$_{min}$]$_{0-4 h}$); 2. ①$p < 0.05$ (0-0.5,1,1.5,2h) ②,③$p < 0.05$; 3. ND
McVey, 2012, USA [32]	RCT(cross-over)*	Type 1 diabetes, 22(22/22)	A. Hollow MNs	B. SC; C. Placebo ID	Periumbilical abdominal wall	8 (ND, washout periods of 3~14 days)	[0~360 min after treatment] 1. PD (Glucose analyzer) ①time in range ②AUG BG ③BG ④BG$_{mean}$ ⑤BG$_{max}$; 2. PK (Glucose analyzer); 3. Intrasubject and intersubject variability ①PK ②PD; 4. Pain (VAS) ①Insertion ②Infusion	[A vs B] 1. ①NS ②$p < 0.05$ (0-4h, 0-6h) ③$p < 0.05$ (2,4,6h) ④$p < 0.05$ (0-4h, 0-6h) ⑤$p < 0.05$ (0-6h); 2. NS; 3. ①$p < 0.05$ (except C$_{max}$: NS) ②$p < 0.05$; 4. $p < 0.05$ (①A>B ②B>A)
								[A vs C] 1~3. NS; 4. $p < 0.05$ ①NS ②C>A
Norman, 2013, USA [33]	RCT(cross-over)*	Type 1 diabetes, 16(16/16)	Hollow MNs	SC	Abdomen	2 (ND, washout periods of separate days)	[15~240 min after treatment] 1. Pain (VAS) ①Insertion ② Infusion; 2. Onset and offset time; 3. Insulin absorption coefficient; 4. Insulin elimination coefficient; 5.	1. ①p=0.005 ②NS; 2. $p < 0.05$; 3. $p < 0.05$; 4,5. NS

							Insulin AUC	
Rini, 2015, USA [34]	RCT(cross-over)*	Type 1 diabetes mellitus patients, 28(28/28)	Hollow MNs	SC	Abdomen	2 (multi-wk, washout periods of over 3 days)	[0~4h after treatment] 1. PK endpoints ①T_{max} ② Onset&Offset ③C_{max} ④Insulin AUC; 2. PD endpoints ①AUC-BG ②BG ③BG_{avg} ④BG_{max} 3. Variability ①Intra- ②inter-subject; 4. Perception endpoints ①Self-rated pain (VAS) ②Acceptability and preference	1. ①~③$p < 0.01$ ④$p < 0.05$ (0-1,1.5h); 2. $p < 0.05$ (①0-1,1.5,2h, ②0-1h, ③0-1.5,2h, ④0-1,1.5,2h); 3. ①$p < 0.05$ ②NS 4. ①ND ②NS
Kochba, 2016, Israel [35]	RCT(cross-over*	Type 2 diabetes , 14(a.3/b.6/c.5) (a. Standard meal condition/ b,c. Fasting condition)	Hollow MNs	SC	Lower abdomen (right)	a, b. 1 (4~14days, washout periods of 4~14days) c. 2 (4~14days, washout periods of 4~14days)	[0~6h after treatment] 1. PK ①T_{max}, ②C_{max} ③Onset ④AUC; 2. PD ①Insulin AUC ②Glucose AUC; 3. The relative bioavailability; 4. Pain (VAS) ①Insertion ②Infusion	[Standard meal and fasting condition] 1. ①,③$p < 0.05$ ②,④NS; 2. ①$p < 0.05$ ②ND 3. NS; 4. ①NS ②$p < 0.05$ (Int<Con) [Only standard meal condition] 1~3. ND; 4. ①NS ②$p < 0.05$ (Int<Con) [Only fasting condition] ①, ③$p < 0.05$ ②,④NS; 2. ①$p < 0.05$ ②$p < 0.05$ (4-6h); 3. NS; 4. ①NS ②$p < 0.05$ (Int<Con)
					Others			
Cosman, 2010, USA [36]	RCT	Postmenopausal osteoporosis 165(A.34/B.32/C.33/D.33/E.33)	A. MAP (20μg TPDP); B. MAP (30μg TPDP); C. MAP (40μg TPDP)	D. SC (Injection pen); E. Placebo patch	A~C,E. The lateral abdomen (alternating left and right sides on a daily basis); D. The abdomen or thigh	28 (28-day, daily)	[6-mon after final treatment] 1. BMD (DXA) ①lumbar spine; ② left total hip; ③femoral neck; ④left forearm; 2. Bone formation marker ①serum P1NP; ②serum CTX; 3. Pharmacokinetic ①AUC; ②C_{max}	[A,B,C vs D] 1. NS; 2,3. ND [A,B vs E] 1. ①$p < 0.001$ ② NS ③,④NS; 2,3. ND [C vs E] 1. ①$p < 0.001$ ②$p < 0.05$ ③,④NS; 2,3. ND
Daddona, 2011, USA [37]	RCT	Osteoporosis, 165(A.33/B.33/C.33/D.33/E.33)	A. MAP (PTH 20μg); B. MAP (PTH 30μg); C. MAP (PTH 40μg)	D. SC (Injection pen); E. Placebo patch	Abdomen, thigh or arm	About 180 (6-mon, daily)	[At 6-mon] 1. Estimates of AUC; 2. Estimates of C_{max}; 3. BMD ①lumbar spine (after 6-mon); ②left total hip (after 6-mon)	[A,B vs D] 1,2. ND; 3. ①,② NS [C vs D] 1,2. ND; 3. ①NS ② $p < 0.05$ [A,B vs E] 1,2. ND; 3. ①$p < 0.05$ ② NS [C vs E] 1,2. ND; 3. ①$p < 0.05$ ②$p < 0.05$

Spierings, 2018, USA [38]	RCT	Migraine, 365(A.90/B.92/C.92/D.91)	A. MAP (zolmitriptan 1 mg); B. MAP (zolmitriptan 1.9 mg); C. MAP (two zolmitriptan 1.9 mg)	D. Placebo patch	The upper arm	A,B,D. 1 (48-h, 1-day); C. 2 (48-h, 1-day)	[2~48h after final treatment] 1. Pain freedom rate (①after 2h; ②2-24h; ③2-48h); 2. Pain relief rate (①2-24h; ②2-48h); 3. MBS freedom rate (after 2h); 4. Patient rate (after 2h) ①Photophobia-free; ②Phonophobia-free; ③Nausea-free; ④Took rescue medication	[A,B vs D] 1,2. $p < 0.05$; 3. NS; 4. $p < 0.05$ (①), NS (②~④) [C vs D] 1,2. $p < 0.05$; 3. $p < 0.05$; 4. $p < 0.05$ (①,③), NS (②,④)

AHA, Alpha hydroxyl acid; ALA, aminolevulinic acid; AUC, area under the curve; $AUC_{10\text{-}360}$, AUC from 10 to 360 min; BG, blood glucose; BMD, bone mineral density; bOPV, bivalent oral poliovirus vaccine; BoNT/A, botulinum toxin A; CCT, clinical control trial; Con, control group; DXAM dual-energy x-ray absorptiometry; CTX, C-terminal cross-linked telopeptide of type 1 collagen; ECCA, echelle d'evaluation clinique des cicatrices d'acne; ED, epidermal; EGF, epidermal growth factor; f-IPV, fractional dose inactivated poliovirus vaccine; GIRs, glucose infusion rates; GMT, Geometric mean titers; GPS, Global photodamage score; HA, haemagglutination; HAI, haemagglutination inhibition; h, hour; HDSS, hyperhidrosis disease severity scale; HI, haemagglutination inhibition; HIV, human immunodeficiency virus; ID, intradermal injection; imp, improvement; IL, insulin lispro; IM, intramuscular injection; inj., Injection; Int, intervention group; IPV, inactivated poliovirus vaccine; ITA°, individual typology angle; MAL, methyl 5-aminolevulinic acid; MAP, microneedle array patch; MBS, bothersome migraine symptom; MI, melanin index; mom, month; MJ, micronejet; MN, microneedle; MRF; microneedle radiofrequency; MTS, microneedle therapy system; ND, not described; NS, not significant; OPV, oral poliovirus vaccine; PGA, physician's global assessment; PaGA, patient's global assessment; PD, pharmacodynamic; PK, pharmacokinetics; POSAS, patient and observer scar assessment; PPG, pharmacodynamic postprandial glycemia; PTH, parathyroid hormone; PV, poliovirus type; P1NP, procollagen type 1 n-terminal propeptide; RCT, randomized control trial; RHI, regular human insulin; SC, Subcutaneous injection; SO, soulvia; TEWL, transepidermal water loss measurement; $tGIR_{max}$, time to maximum GIR; TIV, trivalent inactivated influenza vaccine; tOPV, trivalent oral poliovirus vaccine; TPTD, teriparatide; VAS, visual analog scale; wk, week; VNA, virus neutralizing antibody; *, These studies shown in which both intervention and control were applied to different areas of a patient (e.g., treatment and control interventions were applied to the left and right faces of one subject, respectively).

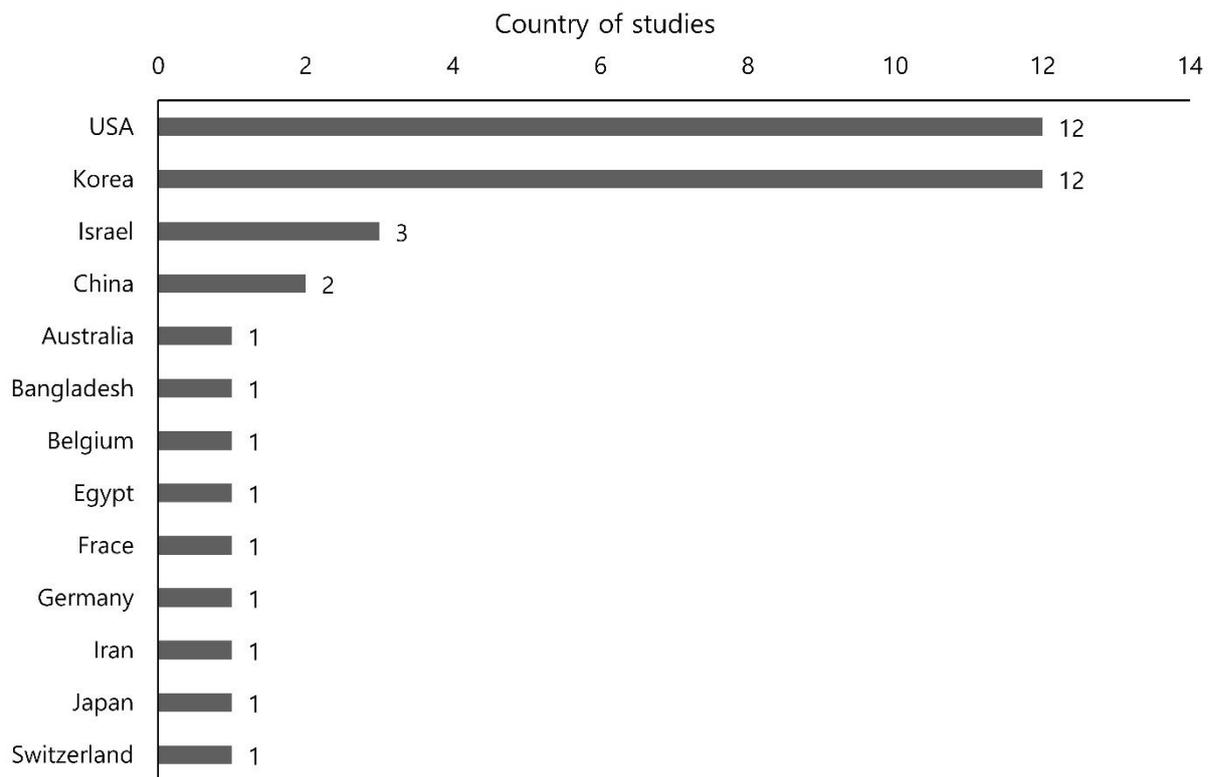**Table S3.** Type of adverse events reported in each study.

Disease.	Author, Year	Disorder	Intervention	Control	Type of AEs		Grade
					Local	Systemic	
Scar	Khater, 2016 [1]	Striae distensae	MTS	CO2 laser	Int&Con) Erythema, PIH	None	Grade 1
	Busch, 2018[2]	Hypertrophic burn scar	MTS	No treatment	Int&Con) Pruritus	None	Grade1
	Ryu, 2013 [3]	Striae distensae	MRF	CO2 laser	Int&Con) PIH, Pruritus, Int) Pain	None	Grade 1
	Chae, 2014 [4]	Atrophic acne scar	MRF	Er:Glass fractional laser	Int&Con) Erythema, Edema, Dryness Con) PIH, Induce acne vulagris	None	Grade 1
Facial wrinkle	Jeon, 2013 [5]	Periorbital static wrinkles	MRF	BoNT/A	Int) Bleeding, Bruising, PIH, Pain	None	Grade 1
	Lu, 2017 [6]	Periorbital/nasolabial wrinkles	MRF	Superficial insertion	Int&Con) Crusting, Erythema, Petechia, Edema	None	Grade 1
	Lee, 2016 [7]	Periorbital wrinkles	MAP	Placebo patch	ND	ND	ND
	Hong, 2018 [8]	Periorbital/nasolabial wrinkles	MAP	No-treatment	None	None	None
Skin care	Kim, 2009 [9]	Facial skin condition	MTS	Alpha hydroxyl acid peeling	Int) Stinging, Flush, Flaky skin, Burn Con) Flush, Flaky skin, Burn, Stinging on eyes, Itching	None	Grade 1
	Choi, 2011 [10]	Facial skin condition	MTS	High frequency treatment	ND	ND	ND
	Kim, 2016 [11]	Facial hyperpigmentation	MAP	Placebo patch	Int&Con) Erythema	None	Grade 1
	Park, 2017 [12]	Fitzpatrick skin type	MAP	Whitening essence	None	None	None
Alopecia	Yoo, 2010 [13]	Alopecia areata	MTS	MAL cream	Int&Con) Erythema Int) Pain	None	Grade 1
	Bao, 2017 [14]	Androgenetic alopecia	AMTS	Minoxidil (topical)	Int) Eczema, Increased Scurf, Auricular Lymph node, Enlargement of cervical or posterior, Pain Con) Seborrheic dermatitis, Itching, Eczema	Int) Infection	Grade 1

Actinic keratoses	Petukhova, 2017 [15]	Actinic keratoses	MTS	Placebo roller	Int&Con) Pain	ND	Grade 1
	Spencer, 2016 [16]	Actinic keratoses	MTS	ALA	ND	ND	ND
Skin (others)	Shin, 2012 [17]	Acne	MRF	CO2 laser	Int&Con) Erythema, Oedema, Pain Con) Hyperpigmentation	None	Grade 1
	Fatemi Naeini, 2015 [18]	Axillary hyperhidrosis	MRF	Placebo MRF (standby mode)	Int&Con) Swelling, Redness, Erythema, Pinpoint bleeding, PIH, Tingling, Numbness	None	Grade 1
	Ryu, 2018 [19]	Multiple warts	MAP	Cryotherapy	Int&Con) Hyperpigmentation, Scar, Nail dystrophy, Delayed response, Pain Int) Erythema	Int&Con) Infection	Grade 1
Vaccine delivery	Hirobe, 2015 [20]	Influenza vaccine	MAP	SC	Int&Con) Erythema, Purpura, Pigmentation, Induration	Int&Con) Fever	Grade 1
	Rouphael, 2017 [21]	Influenza vaccine	MAP	1. IM 2. Placebo patch	Int&Con) Pain Int) Induration, Erythema, Tenderness, Pruritis Con1) Induration, Tenderness, Pruritis Con2) Tenderness, Pruritis	Int&Con) Fatigue, Myalgia, Shivering or shaking body movements, Nausea, Headache, Arthralgia, Malaise Int) Fever, Sweating Con1) Sweating	Grade 1
	Fernando, 2018 [22]	Influenza vaccine	MAP	1. IM 2. Placebo patch 3. Placebo IM	Int) Application site pruritus, Axillary pain, Sinusitis, Oropharyngeal pain Con) Oropharyngeal pain, Throat irritation	Int) Headache, Lymph-adenopathy, viral URTI, Myalgia Con) Headache, Fatigue, Upper respiratory tract infection (URTI)	Grade 1
	Damme, 2009 [23]	Influenza vaccine	Hollow MN s	IM	Int&Con) Erythema, Swelling, Induration, Pain Int) Discoloration, Pruritus, Desquamation	Int&Con) Headache, Malaise, Myalgia	Grade 1
	Laurent, 2010 [24]	Influenza vaccine	Hollow MNs	1. IM 2. ED	Int&Con) Erythema, Induration, Itching, Swelling Int&Con1) Pain Con)The deltoid muscle pain	Int) Myalgia, Headache, Flu-like symptoms	Grade 1
	Frenck, 2011 [25]	Influenza vaccine	1. Hollow MNs (6μg HA/strain)	1. IM 2. ID	Int&Con) Itching, Redness, Swelling, Pain	Int&Con) Headache, Fever Int2) Acute disseminated encephalomyelitis*	All - Grade 1

			2. Hollow MNs (9μg HA/strain)	(Mantoux)			* - Grade 3
	Levin, 2014 [26]	Influenza vaccine	Hollow MNs	1. ID (Mantoux) 2. IM	Int&Con) Post-vaccination pain, Induration, Erythema	ND	Grade 1
	Anand, 2015 [27]	Poliovirus vaccine	Hollow MNs	1. tOPV (Oral) 2. bOPV (Oral) 3. IPV (IM)	None	Int) Allergic rhinitis, Allergic conjunctivitis, Chicken pox, Common cold, Measles, Tinea capitis, Acute ottis media, Fever with no infectious focus, Fever probably related to pentavalent, Infective dermatitis, Scabies, Diarrhoea*, Pneumonia**, Infantile seizures**, Sudden infant death syndrome** Con1) Sudden infant death syndrome, Acute gastroenteritis, Allergic conjunctivitis, Boil, Common cold, Fever, Diarrhoe*, Pneumonia* Con2) Common cold, Fever, Oral candidiasis, Skin rash, Acute gastroenteritis*, Pneumonia* Con3) Common cold, Fever, Oral candidiasis, Diarrhoea*, Meningits*	Grade 1 * - Grade 3 ** - Grade 5
	Troy, 2015 [28]	Influenza vaccine	Hollow MNs	IM	Int&Con) Swelling, Tederness, Redness Int) Itching	Int&Con) Rash, Fever	Grade1
	Levin, 2016 [29]	Influenza vaccine	1. Hollow MNs (7.5 μg HA, MJ) 2. Hollow MNs (15 μg HA, MJ) 3. Hollow MNs (inactivated 15 μg HA, SO)	1. IM (15 μg HA) 2. IM (45 μg HA) 3. IM (15 μg HA with adjuvant)	Int&Con) Erythema, Ecchymosis, Induration Int2) Polymyalgia rheumatic*	Int&Con) Fever, Shivering, Malaise Con3) Death**	Grade 1 * - Grade 3 ** - Grade 5
	Vescovo, 2017 [30]	The rabies vaccine delivery	Hollow MNs	1. ID (Mantoux) 2. IM	Int & Con) Redness, Pruritus, Pain	Int&Con) Headache, Gastrointestinal disorder, Asthenia, Dizziness, Malaise, Nausea, Myalgia	Grade 1
Insulin delivery	Pettis, 2011 [31]	Type 1 diabetes	Hollow MNs	SC	Int&Con) Pain Int) Edema	Int&Con) Headache, Diarrhea, Hypoglycemic episodes	Grade 1
	McVey, 2012 [32]	Type 1 diabetes	Hollow MNs	1. SC 2. Placebo MNs	Int&Con) Erythema, Edema, Pain	Int&Con) Headache	Grade 1
	Norman, 2013 [33]	Type 1 diabetes	Hollow MNs	SC	Int&Con) Blebs, Pain	None	Grade 1
	Rini, 2015 [34]	Type 1 diabetes mellitus patients	Hollow MNs	SC	Int&Con) Erythema, Edema, Pain	Int&Con) Headache, Dizziness, Nausea, Vomiting	Grade 1
	Kochba,	Type 2 diabetes	Hollow MNs	SC	Int&Con) Pain	Int&Con) Hypoglycemia	Grade 1

	2016 [35]						
Others	Cosman, 2010 [36]	Postmenopausal	MAP	1. SC 2. Placebo patch	Int&Con) Erythema	Int&Con) Arthralgia/pain in extremities, Dizziness, Headache, Nausea, Serum calcium elevation, Hypercalcemia*, Hypercalciuria* Int) Urine/creatinine ratio increased*, Nephrolithiasis* Con) Crystal urine, Hypotension, Syncope, Blood calcium decreased*	All – Grade 1 * - Grade 2
	Daddona, 2011 [37]	Osteoporosis	MAP	1. Injection pen 2. Placebo patch	Int & Con 2) Erythema	None	Grade 1
	Spierings, 2018 [38]	Migraine	1. MAP (1mg zolmitriptan) 2. MAP (1.9mg zolmitriptan) 3. MAP (3.8mg zolmitriptan)	Placebo patch	Int&Con) Erythema, Bruise, Pain, Swelling/edema Int) Hemorrhage, Redness Int 3) Bruise*, Pain*	Int&Con) Paresthesia Int) Dizziness, Muscle tightness, Nausea Int 3) Muscle tightness*	All - Grade 1 * - Grade 2

*, not grade 1 AE; AE, Adverse event; AMTS, auto microneedle therapy system; bOPV, bivalent oral poliovirus vaccines; Con, control group; ED, epidermal; HA, haemagglutination; HIV, human immunodeficiency virus; ID, intradermal; Int, intervention group; IM, intramuscular injection; IPV, inactivated poliovirus vaccine; MAL, methyl 5-aminolevulinic acid; MAP, microneedle array patch; MJ, micronjet; MTS, microneedle therapy system; MN, microneedle; MRF, microneedle radiofrequency; NA, Not applicable; None, No adverse events; PIH, post inflammatory hyperpigmentation; SC, subcutaneous injection; SO, soulvia; tOPV. trivalent oral poliovirus vaccines; TPTD, teriparatide.

Figure S1. Number of studies included by country.

Figure S2. Risk of bias summary of randomized controlled trials (RCT).

Figure S3. Risk of bias summary of controlled clinical trials (CCTs).

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