Table F-1. Risk of bias in RCTs

| Study | Adequate generation of a randomized sequence reported | Adequate allocation concealment reported | Group similarity at baseline | Adequate blinding of PATIENTS reported | Adequate blinding of PROVIDERS reported | Adequate blinding of OUTCOME ASSESSORS reported | Intention to treat analysis? | Incom-plete results data | Incomplete results data: Differential missingness  | Adverse events (of interest) precisely defined | Selective Reporting  | Overall, by outcome |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Abbade 2015 (Conference abstract) (Brazil) | No Data | No Data | Yes | No | No | No Data | Yes | No | No | No Data | No | Moderate |
| Al-Niaimi 2015 26157307 (UK) | Unsure | Yes | Yes | No | No | Yes | No | Yes | Yes | No |  (12 month results mentioned in the protocol not given; recurrence rates not given by arm; only 1 AE given) | cosmetic outcomes: low recurrence: moderate to high |
| Allen 1979 298425 (UK) | Yes ("subjects randomly assigned in a coded, controlled trial.") | Yes ("randomly coded allocation of treatment") | No Data (No Table 1 / patient characteristics reported.) | Yes (Subjects could not be blinded to treatment allocation (Cryotherapy vs. Radiotherapy)) | No Data (No mention is made of blinding providers; Review Authors do not discuss whether this would impact the outcome.) | No Data (No mention is made of blinding outcome assessors; Review Authors do not discuss whether this would impact the outcome.) | No Data (No dropouts reported.) | No Data (Only Recurrence was reported, but it was reported completely for both arms of the trial.) | No Data (See above) | No Data (No Adverse Events were reported) | Low RoB (Outcome of interest, recurrence, was reported by arm.) | High |
| Alpsoy 1996 8708151 (Turkey) | Unsure | Unsure | Yes | Unsure | Unsure | Unsure | Yes | No | No | Yes |  | High |
| Arits 2013 23683751 (Netherlands) | Yes | Yes | Yes | No (patients were not blinded) | No (caregivers were not blinded) | Yes (all outcome assessors (except for AEs, which were assessed by patients) were blinded) | Yes | No | No | Yes | No | Low |
| Avril 1997 9218740 (France) | Unsure (method of randomization not reported) | Yes | Yes | No (The lack of blinding is concerning for patient and physician reported cosmetic outcomes, but they also report outcomes from third-party blinded assessors) | No (The lack of blinding is concerning for patient and physician reported cosmetic outcomes, but they also report outcomes from third-party blinded assessors) | No (The lack of blinding is concerning for patient and physician reported cosmetic outcomes, but they also report outcomes from third-party blinded assessors) | Unsure (ITT not reported, low number of dropouts) | Yes (23% and 27% lost to followup by mean followup time of 41 months) | No (similar rates between arms) | No (they were reported, but not well defined) |  (Neither paper reported AEs adequately) | High |
| Basset-Seguin 2008 18693158 (13 centers in 7 european countries) | Unsure | Yes | Yes | No | No | Unsure | No | No | No | Yes |  | Low to moderate for all outcomes |
| Bath-Hextall 2014 24332516 (UK) | Yes | Yes | Yes | No | No | Yes | Yes (Modified ITT: all randomized patients who received at least 1 application of imiquimod or surgery and for whom the outcome was available) | Yes | No | Yes | No | Low |
| Berroeta 2007 17573890 (United Kingdom) | Yes | Yes | No Data | No | No | Yes | Yes | No | No | Yes | Yes (Said they measured at multiple timepoints but only reported 1 year) | Moderate  |
| Beutner 1999 10570388 (USA) | No Data | No Data | No (Group sizes are very small) | Unsure | Yes | No Data | Yes (no dropouts or crossover) | No | No | Yes | No | Moderate to high due to small sample size and baseline differences |
| Brinkhuizen 2016 27067393 (Netherlands) | Yes | Yes | No (superficial not similar, nodular similar enough) | No | No | Yes | Yes | No | No | Yes | None immediately apparent | Low to moderate |
| Butler 2009 19018814 (texas, usa) | Yes | Yes | Yes | Yes | Yes | Yes | No (3 patients who failed to complete the study were included as treatment failures. this is not ITT.) | No | No (3 patients in imiquimod group and 0 patients in vehicle groupp) | Yes | No | Low for all outcomes |
| Cai 2015 25899562 (china) | Unsure | Yes | Yes | Unsure | Yes | Yes | Unsure (study states: "patients randomly assigned to two groups according to their hospital identification number" did not mention a specific computer generator) | No | No | No (no table for adverse events; study loosely describes ae in the body of the text for study arm) |  | Low for efficacy; high for AEs |
| Carija 2016 27516420 (Croatia) | No | No | Yes | unsure | Yes | Yes | No | No | No | Yes | Yes | Moderate for all outcomes |
| Choi 2016 26551044 (Korea) | Unsure (did not elaborate on how subjects were randomized) | Yes | Yes | Yes | Yes | Yes | No (five subjects dropped out prematurely for unrelated reasons to study and were analyzed as treatment failures. discussed with gaelen who did not think it effected outcomes or data based on bounding analysis.) | No | No | Yes | No | Low for all outcomes |
| Choi 2017 28199463 (Korea) | Yes | No | Yes | No | No | Yes | Yes | No | No | Yes | No | Low for all outcomes |
| Cornell 1990 2229497 (U.S.) | Yes | No Data | Yes (Location might be slightly different, disadvantages the treatment group) | Yes | No | Yes | Yes | No | No | Yes | No | Low for all outcomes |
| Edwards 1990 2107219 (U.S.) | Unsure (not reported; randomization done in blocks by lesion type (superficial or nodular)) | Unsure (not reported) | Unsure (baseline data not reported) | Unsure (not reported) | Unsure (not reported) | Unsure (not reported) | Yes | No | No | Yes |  (Adverse events and cosmetic outcomes were not presented by arm.) | This paper lacks detail on study design, so it is unclear whether it was properly conductedModerate to high  |
| Edwards 1990 2383027 (U.S.) | Unsure (not reported; subjects randomized in blocks based on lesion type) | Unsure (not reported) | Unsure (no baseline details given) | Yes | Yes | Yes | Yes (no drop outs, no crossovers) | No | No | No (Adverse events were not defined and were not given by arm) |  (There appears to be some selective reporting: cosmetic outcomes were only reported in a subset of patients and not by arm, adverse events were not reported by arm. <-seems to be true in all studies) | This is an older study and a very short report, so things may have been done right but not adequately reportedModerate to high  |
| Eigentler 2007 17610993 (Germany) | No Data | No Data | Unsure | No | No Data | No Data | No | No | No | Unsure (partial reporting, but they say there's no difference between arms) |  | Moderate to low |
| Eimpunth 2014 (Conference abstract) (unclear) | No Data | No Data | No Data | No | No Data | No Data | Yes | No | No | No |  (probably) | It is very difficult to assess quality based on the abstract alone |
| Foley 2009 20064185 (U.S. and australia) | Yes | Yes | Unsure (They did note a significant difference btw groups in the distribution of Fitzpatrick skin phototype (p<0.05), largely caused by greater proportion of patients with skin type 1 in the MAL group) | Yes | Yes | Yes | No (3 dropouts (2 in MAL and 1 in placebo) inconsistent and unclearly presented.) | No | No | Yes | No | Low for all outcomes |
| Garcia-Martin 2011 21242584 (Spain) | Unclear RoB | Unclear RoB | Low RoB | High RoB | Moderate RoB | Unclear RoB | Low RoB | Low RoB |  | Low RoB |  (opthomologist rated cosmetic outcome prespecified in the methods but not reported in the results) | Low to moderate due to lack of blinding |
| Geisse 2002 12196749 (U.S.) | Yes | Yes | Yes | Yes | Yes | Yes | Yes | No | No | Yes (Some AEs were not reported for vehicle groups) |  (not immediately apparent) | Low for all outcomes |
| Geisse 2004 15097956 (U.S.) | Yes | Yes | No (ages and locations of tumors differ) | Yes | Yes | Yes | Yes | No | No | No (AE reporting was there, but inconsistent (sometimes by arm, sometimes with numbers, etc)) |  (I don't see any sign of overt selective reporting) |  Low; moderate for AEs |
| Haak 2015 24903544 (Denmark) | Yes | Yes | Yes | No | No | Yes (except patient cosmetic outcomes) | Yes | No | No | Yes |  (none immediately obvious) | Low for all outcomes |
| Hall 1986 3514075 (UK) | No (Not mentioned how randomized) | No (Not mentioned) | No (Difference in size and location) | No (Not possible to blind) | No (Not possible to blind) | No (Not mentioned) | No (Only analyzed patients with follow-up data) | Unsure (Only gives dropouts for whole study not per group) | No Data (Only gives dropouts for whole study not per group) | No | No | Unsure Differential missingness not reported |
| Ko 2014 24102369 (Korea) | Unsure | No | Yes | No | Unsure | Yes | Unsure (ITT population was 19. they had one dropout (unclear how many lesions) who violated protocol and counted as treatment failure. bc the exact number of lesions randomized for the 19 pts was not abailable for ITT eval, pp was used for data extraction.) | No | No | Yes |  (not immediately apparent) | Low |
| Kuijpers 2006 16865869 (Netherlands) | Yes | Yes | Maybe (4 superficial BCC in surgery arm. All others nodular.) | No (Not possible) | No (Not possible) | Unsure (3rd blinded party did assessments "where possible") | No (Not true intention to treat, completer analysis) | Yes (13/51 tumors in the cryo group lost to follow-up2/49 in surgical group) | Yes (Cryo group had 13 missing at 5 years vs. 2 in excision group) | No |  (Missing systematic reporting of AEs) | Moderate to high due to missingness |
| Kuijpers 2007 17451581 (Netherlands) | No Data ("randomly assigned" is only mention) | Unsure | Yes (seem similar enough) | Unsure | Unsure | Yes (pathologist was blinded) | Yes (no dropouts) | No | No | No | No (no reporting of adverse events other than pain) | Low for effectiveness outcomes and moderate for AEs |
| Marks 2001 11312429 (Australia and New Zealand) | No (Not reported) | No (Not reported) | Unsure (Minimal data given in table 1) | No (Open-label) | Unsure (Open-label) | Unsure (Open-label) | No (Not true ITT but number of dropouts is low) | No | No | Yes |  (Unclear - no protocol available but all outcomes of interest available) | Moderate to high |
| Migden 2015 25981810 (worldwide) | Yes | Yes | Yes | Yes | Yes | Yes | Yes (both ITT and as treated results reported) | No (Very high dropout rate; most due to adverse events. Bounding analysis suggest there is high risk of bias due to dropouts) | No (dropout rates and reasons were similar across arms) | Yes |  (Possible; only a small number (7) of QOL results reported; NCT record does not call for any QOL results.) | Moderate due to dropouts |
| Miller 1997 8996264 (USA) | Unclear RoB (randomization procedure undefined) | Unclear RoB (randomization procedure undefined) | No Data | Low RoB (open label but outcomes aren't likely influenced) | Low RoB (open label but outcomes aren't likely influenced) | Low RoB (open label but outcomes aren't likely influenced) | Unsure (FLAG some drop outs related to treatment) | Yes (drops outs occurred either prior to completion or were unrelated to treatment) | Yes | Low RoB | No (adverse events selectively reported or not stratified, cosmetic outcome not fully reported, histologic clearance is reported fully) | Moderate for clearance, high for other outcomes |
| Morton 1996 8977678 (Scotland) | Unsure (not fully randomized) | Unsure | Yes | No | No | No (only one outcome assessor was reported to be blinded and that outcome was given at the fewest timepoints) | No (per protocol, not too many dropouts for 1 year, unclear for 2 years) | Yes (possibly for long-term) | Yes (possibly for long-term) | Yes |  (It feels like there may be some selective reporting in the aesthetic outcomes) | Low to moderate due to lack of blinding and long term dropouts |
| Morton 2006 16785375 (Europe) | No Data (Not reported) | No Data (Not reported) | Unsure (Lesions size was different; this was accounted for in a regression.) | No (unblinded) | No (unblinded) | No (unblinded) | Yes (no dropouts) | No | No | Yes |  (Does not appear to be any) | Older study with poor reporting. Lack of blinding may affect AE reporting, but unlikely to affect clearance or recurrence high due to poor reporting |
| Mosterd 2008 18717680 (Netherlands) | Yes | Yes | Yes | Yes | No | No | Yes | Yes | No | Yes |  (Aesthetic outcomes only reported in combined recurrent/primary arm. Subgroup analysis for more severe cancers missing followup Ns;) |  Low to maybe moderate because of loss to followup. |
| Mosterd 2008 19010733 (Netherlands) | Yes | Yes | Unsure (Very few baseline details were given. Those that are given are similar.) | No (No blinding) | No (No blinding) | No (No blinding) | Yes | Yes (48 months >30% missingness) | Yes (48 months differential) | No (AEs were not defined) |  (The lack of specificity in AE and baseline data reporting may suggest selective reporting) |  Moderate for early followup and high for later followup |
| Orenberg 1992 1430394 (USA) | Unclear RoB | Unclear RoB | No | Low RoB | Low RoB | Low RoB | Unsure (No dropouts/protocol breaks reports) | No | No | High RoB | Yes | High, Lots of uncertainty, very small study |
| Patel 2006 16713457 (United Kingdom) | Yes | Yes | No (legion size different between groups) | Yes | Yes | Yes | No | Yes (3/15) | Yes (20% in one arm, no dropout in other arm) | No (not well-defined, not reported by arm) |  |  High, blinding is good but groups are not similar, there is differential missingness, and outcomes are not reported by arm |
| Rhodes 2004 14732655 (Europe) | Yes | Yes | No (location of lesions differed significantly; this matters because a subgroup analysis by location of lesion was done) | No | No | No (could lead to bias as lack of cure was established clinically and both investigators and patients assessed cosmetic outcomes) | No (per protocol analysis was done. The authors state that an ITT analysis was nearly identical) | Yes (No for the early followup; yes for followup beyond 1 year) | No | Yes |  (hard to tell) |  High, especially given that the funding came from a PDT source |
| Salim 2003 12653747 (UK) | No (Not reported) | No (Not reported) | No (Lesion location not similar. Other characteristics not provided) | No (Not reported) | No (Not reported) | No (Not reported) | Yes | No | Yes (Dropouts occurred only in the 5-FU group) | No |  (Did not report AE assessments from each visit) | High risk of bias due to between-group differenceslocation and selective reporting of AEs |
| Salmanpoor 2012 (Iran) | No (Not reported) | No (Not reported) | No Data (No Table 1 or other comparison) | Unsure (Not reported) | Unsure (Not reported) | Unsure (Not reported) | Yes (No dropouts reported) | No (No missing data reported) | No (No missing data reported) | Not Applicable (No AEs discussed) |  (No AEs reported) | High |
| Schleier 2007 25047438 (Germany (Friedrich-Schiller University Jena)) | Yes | No | Yes | Yes | Yes | Yes | Unsure | No |  | Yes (pain specifics unavailable) |  | Moderate for all outcomes |
| Schulze 2005 15888150 (Europe) | Yes (randomized to imiquimod or vehicle in a 1 : 1 ratio according to a computer-generated randomization schedule) | Yes (Study personnel remained blinded to the randomization until the database was complete and locked.) | Yes | Yes (Subjects, study personnel and the sponsor’s clinical research team were blinded to study cream identity and treatment assignment) | No | Unsure | Yes | Yes | Yes | No | Yes | Low |
| Shumack 2002 12224977 (12 weeks) (Australia and New Zealand; And United States) | No (92 patients randomized to Imiquimod and placebo according to the dosing scheme: - once daily for 3 days per week (20 Active, 8 Vehicle)-once daily for 5 days per week (23 A, 6 V)- once daily for 7 days per week (21 A, 10 V)) | No Data (method of allocation concealment was not reported) | No (Twice daily for 7 days per week group (4 active, 0 control) Mean age is different from range of age in other groups and combined vehicle) | Yes | No Data ("double blind") | No Data ("double blind") | Yes (15 were discontinued from the study. Post treatment excision results were obtained for 11 of these. Intention to Treat was reported.) | No (Clearance outcome was partially reported. Reported for combined vehicle separate from dosing regimen groups, where only results of imiquimod patients were reported.) | No | No (AE were defined but # of counts within each arm was not completely reported.) | Yes (AE were defined but # of counts within each arm was not completely reported.) | Low for clearance outcomes, unclear for AEs |
| Shumack 2002 12224977 (6 weeks) (Australia and New Zealand; And United States) | Yes (99 patients randomized to Imiquimod and placebo according to the dosing scheme: - once daily for 3 days per week (32)-twice daily for 3 days per week (31) - once daily for 7 days per week (35)- twice daily for 7 days per week (1)) | No Data | No (Noticeable difference in age for Twice daily for 7 days/ week arm (n=1)) | Yes | No Data | No Data | Yes (9 patients were discontinued from the study, but only 4 did not undergo post-treatment excision5 of 99 enrolled did not undergo post treatment excision.ITT not reported.) | No | No | Yes | No | Low Adverse events reported but not for every arm |
| Siller 2010 20546215 (8 private dermatology clinics Australia) | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Unsure | No | Yes |  | Low for all outcomes |
| Spencer 2006 16393600 (United States) | No Data (randomization not reported) | No Data | Unsure (very low n) | No Data | No Data | No (blinding not reported) | Yes (no dropouts) | No | No | No | No (not all time points reported.) | High risk of bias |
| Sterry 2002 12452875 (nodular) (Europe) | Yes | Yes | Yes | No | No | Unsure | No | No | Yes | No (Few AEs reported by arm; in general unclear AE reporting) |  (Not immediately evident) | Low for efficacy and moderate to high for AEs |
| Sterry 2002 12452875 (superficial) (Europe) | Yes | Yes | No | No | No | Unsure | No | No | Yes | No (Few AEs reported by arm; in general unclear AE reporting) |  | Low to moderate for efficacy and moderate to high for AEs |
| Szeimies 2008 18624836 (United Kingdom/Germany/Switzerland/Australia) | Yes | Yes | Yes | No | No | No | Unsure (per protocol analysis) | No | Yes (some outcomes) | No |  | Low to moderate  |
| Thissen 2000 10940063 (Netherlands) | No Data | No Data | Yes | No (Not possible to blind patients to treatment allocation (cryosurgery vs. surgical excision)) | No Data (It is not reported if providers were blinded, might be high RoB for clinical recurrence outcome) | Unsure (cosmetic results were independently assessed by 5 professionals who were "not involved in the trial and who were blinded to the treatment") | Yes (few drop-outs not reported by arm (3 did not appear for control visits and 1 died), not related to treatment or outcome) | No (Clearance is fully reported by arm.) | No | Yes (AEs: secondary wound infections; moderate to severe swelling of treated area. (Reported by Arm)) | No | Moderate to high because of blinding only |
| Torres 2004 15606733 (loma linda, CA; boston, MA) | Yes (computer-generated schedule) | No | Yes | Yes | Yes | Unsure (histologist) | Yes | No |  | No (Not well reported) | No (probably not) | Low for all outcomes |
| Tran 2012 22511036 (US) | No Data | No Data | No (groups were not similar at baseline, though the differences were not statistically significant (probably because of the small sample size)) | Yes | No | No | Yes | No | No | Yes |  (unclear) | Moderate to high due to nonsimilar baselines |
| van der Geer 2012 22385074 (Netherlands) | Yes | Yes | Yes | No (no mention of blinding) | No (no mention of blinding) | No (High RoB, no mention of blinding, and only clinical clearance outcome) | Yes | No | No | Yes |  (none that i could spot easily) | Moderate |
| Wang 2001 11298545 (England) | No Data | Unsure | Unsure (The two treatment groups were comparable concerning medical history of the patients and status at the medical examination.) | No (No blinding regimen was possible due to the nature of the treatment procedures.) | No (No blinding regimen was possible due to the nature of the treatment procedures.) | No Data | Yes | No | No | Yes |  | Low to moderate due to poor reporting |
| Wettstein 2013 23566745 (Switzerland) | Yes | No Data | Yes | Yes | Yes | No Data | Yes | No | No | Yes |  (Low) | Low |