**Research priorities regarding the use of bisphosphonates: a UK priority setting exercise**

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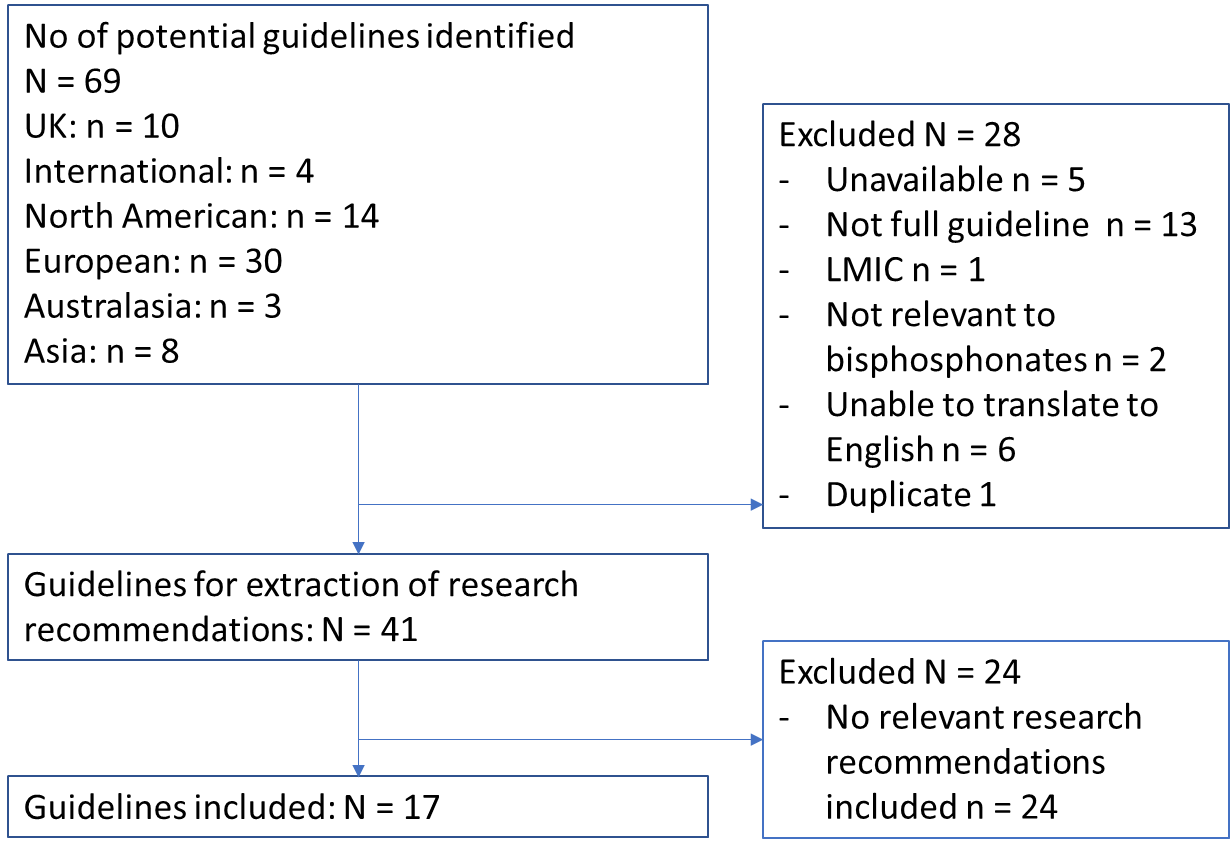
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# Figure 1: Search for Clinical Guidelines results



# Full list of potential guidelines identified (2016-July 2021)

International

Diez-Perez, A., Naylor, K. E., Abrahamsen, B., Agnusdei, D., Brandi, M. L., Cooper, C., Dennison, E., Eriksen, E. F., Gold, D. T., Guañabens, N., Hadji, P., Hiligsmann, M., Horne, R., Josse, R., Kanis, J. A., Obermayer-Pietsch, B., Prieto-Alhambra, D., Reginster, J. Y., Rizzoli, R., Silverman, S., Zillikens, M. C. and Eastell, R. (2017). International Osteoporosis Foundation and European Calcified Tissue Society Working Group. Recommendations for the screening of adherence to oral bisphosphonates. *Osteoporos Int,* **28**(3): 767-774. doi: 10.1007/s00198-017-3906-6

Eastell, R., Rosen, C. J., Black, D. M., Cheung, A. M., Murad, M. H. and Shoback, D. (2019). Pharmacological Management of Osteoporosis in Postmenopausal Women: An Endocrine Society\* Clinical Practice Guideline. *J Clin Endocrinol Metab,* **104**(5): 1595-1622. doi: 10.1210/jc.2019-00221

Rolland, Y., Cesari, M., Fielding, R. A., Reginster, J. Y., Vellas, B. and Cruz-Jentoft, A. J. (2021). Osteoporosis in Frail Older Adults: Recommendations for Research from the ICFSR Task Force 2020. *J Frailty Aging,* **10**(2): 168-175. doi: 10.14283/jfa.2021.4

Shoback, D., Rosen, C. J., Black, D. M., Cheung, A. M., Murad, M. H. and Eastell, R. (2020). Pharmacological Management of Osteoporosis in Postmenopausal Women: An Endocrine Society Guideline Update. *J Clin Endocrinol Metab,* **105**(3). doi: 10.1210/clinem/dgaa048 - specific focus on romosozumab **Not a bisphosphonate**

European

Kanis, J. A., Cooper, C., Rizzoli, R., Reginster, J. Y., Scientific Advisory Board of the European Society for, C., Economic Aspects of, O., the Committees of Scientific, A. and National Societies of the International Osteoporosis, F. (2019). European guidance for the diagnosis and management of osteoporosis in postmenopausal women. *Osteoporos Int,* **30**(1): 3-44. doi: 10.1007/s00198-018-4704-5

Kanis, J. A., Cooper, C., Rizzoli, R., Reginster, J. Y., Scientific Advisory Board of the European Society for, C., Economic Aspects of, O., the Committees of Scientific, A. and National Societies of the International Osteoporosis, F. (2020). Correction to: European guidance for the diagnosis and management of osteoporosis in postmenopausal women. *Osteoporos Int,* **31**(4): 801. doi: 10.1007/s00198-020-05303-5

Kanis, J. A., Cooper, C., Rizzoli, R., Reginster, J. Y., Scientific Advisory Board of the European Society for, C., Economic Aspects of, O., the Committees of Scientific, A. and National Societies of the International Osteoporosis, F. (2020). Correction to: European guidance for the diagnosis and management of osteoporosis in postmenopausal women. *Osteoporos Int,* **31**(1): 209. doi: 10.1007/s00198-019-05184-3

Lems, W. F., Dreinhöfer, K. E., Bischoff-Ferrari, H., Blauth, M., Czerwinski, E., da Silva, J., Herrera, A., Hoffmeyer, P., Kvien, T., Maalouf, G., Marsh, D., Puget, J., Puhl, W., Poor, G., Rasch, L., Roux, C., Schüler, S., Seriolo, B., Tarantino, U., van Geel, T., Woolf, A., Wyers, C. and Geusens, P. (2017). EULAR/EFORT recommendations for management of patients older than 50 years with a fragility fracture and prevention of subsequent fractures. *Ann Rheum Dis,* **76**(5): 802-810. doi: 10.1136/annrheumdis-2016-210289

Pan Arab (check countries)

Jassim, N. A., Adib, G., Abdul Rahman, Y. A., Gorial, F. I., Maghraoui, A., Al Suhaili, A. R., Murtaji, A., Otom, A., Masri, B., Saba, E., Badran, F., Maalouf, G., Saleh, J., El Muntaser, K., Zakraoui, L., Al Izzi, M., Al Ali, N., Sulaimani, R., Abdul Majeed, S. and Al Emadi, S. (2017). Pan Arab Osteoporosis Society Guidelines for Osteoporosis Management. *Mediterr J Rheumatol,* **28**(1): 27-32. doi: 10.31138/mjr.28.1.27 **No Research Recommendations given**

America

Allen, S., Forney-gorman, A., Homan, M., Kearns, A., Kramlinger, A. and Sauer, M. (2017). *Diagnosis and Treatment of Osteoporosis*: Institute for Clinical Systems Improvement,.

Anderson, P. A., Freedman, B. A., Brox, W. T. and Shaffer, W. O. (2021). Osteoporosis: Recent Recommendations and Positions of the American Society for Bone and Mineral Research and the International Society for Clinical Densitometry. *J Bone Joint Surg Am,* **103**(8): 741-747. doi: 10.2106/jbjs.20.01248 **No RRs**

Buckley, L., Guyatt, G., Fink, H. A., Cannon, M., Grossman, J., Hansen, K. E., Humphrey, M. B., Lane, N. E., Magrey, M., Miller, M., Morrison, L., Rao, M., Byun Robinson, A., Saha, S., Wolver, S., Bannuru, R. R., Vaysbrot, E., Osani, M., Turgunbaev, M., Miller, A. S. and McAlindon, T. (2017). 2017 American College of Rheumatology Guideline for the Prevention and Treatment of Glucocorticoid-Induced Osteoporosis. *Arthritis Care Res (Hoboken),* **69**(8): 1095-1110. doi: 10.1002/acr.23279 **No Research Recommendations given**

Buckley. (2017). Erratum: 2017 American College of Rheumatology Guideline for the Prevention and Treatment of Glucocorticoid-Induced Osteoporosis (vol 69, pg 1776, 2017). Arthritis Care Res (Hoboken). doi: <https://doi.org/10.1002/acr.23441>

Buckley, L., Guyatt, G., Fink, H. A., Cannon, M., Grossman, J., Hansen, K. E., Humphrey, M. B., Lane, N. E., Magrey, M., Miller, M., Morrison, L., Rao, M., Robinson, A. B., Saha, S., Wolver, S., Bannuru, R. R., Vaysbrot, E., Osani, M., Turgunbaev, M., Miller, A. S. and McAlindon, T. (2017). 2017 American College of Rheumatology Guideline for the Prevention and Treatment of Glucocorticoid-Induced Osteoporosis. *Arthritis Rheumatol,* **69**(8): 1521-1537. doi: 10.1002/art.40137 **No Research Recommendations given**

Camacho, P. M., Petak, S. M., Binkley, N., Clarke, B. L., Harris, S. T., Hurley, D. L., Kleerekoper, M., Lewiecki, E. M., Miller, P. D., Narula, H. S., Pessah-Pollack, R., Tangpricha, V., Wimalawansa, S. J. and Watts, N. B. (2016). AMERICAN ASSOCIATION OF CLINICAL ENDOCRINOLOGISTS AND AMERICAN COLLEGE OF ENDOCRINOLOGY CLINICAL PRACTICE GUIDELINES FOR THE DIAGNOSIS AND TREATMENT OF POSTMENOPAUSAL OSTEOPOROSIS - 2016. *Endocr Pract,* **22**(Suppl 4): 1-42. doi: 10.4158/ep161435.Gl **Not obtainable**

Camacho, P. M., Petak, S. M., Binkley, N., Diab, D. L., Eldeiry, L. S., Farooki, A., Harris, S. T., Hurley, D. L., Kelly, J., Lewiecki, E. M., Pessah-Pollack, R., McClung, M., Wimalawansa, S. J. and Watts, N. B. (2020). American Association of Clinical Endocrinologists/American College of Endocrinology Clinical Practice Guidelines for the Diagnosis and Treatment of Postmenopausal Osteoporosis-2020 Update. *Endocr Pract,* **26**(Suppl 1): 1-46. doi: 10.4158/GL-2020-0524SUPPL **No Research Recommendations of interest given**

Hauk, L. (2018). Treatment of Low BMD and Osteoporosis to Prevent Fractures: Updated Guideline from the ACP. *Am Fam Physician,* **97**(5): 352-353. No rr

Mettawi, A. S., Soliman, S. S. and Taha, M. E. (2020). Clinician's guide for the management and research of osteoporosis in North African men: a guidelines comparison, a cost-effectiveness analysis, and a local algorithm. *Archives of osteoporosis,* **15**(1): 159. doi: 10.1007/s11657-020-00830-4 **India (LMIC)**

Paci, M., Burks, S. and Wang, M. Y. (2018). Consensus Guidelines for the Treatment of Osteoporosis. *Neurosurgery,* **82**(1): N6-n7. doi: 10.1093/neuros/nyx530 **America? – not a guideline**

Qaseem, A., Forciea, M. A., McLean, R. M., Denberg, T. D. and Clinical Guidelines Committee of the American College of, P. (2017). Treatment of Low Bone Density or Osteoporosis to Prevent Fractures in Men and Women: A Clinical Practice Guideline Update From the American College of Physicians. *Ann Intern Med,* **166**(11): 818-839. doi: 10.7326/M15-1361

Weaver, C. M., Gordon, C. M., Janz, K. F., Kalkwarf, H. J., Lappe, J. M., Lewis, R., O'Karma, M., Wallace, T. C. and Zemel, B. S. (2016). The National Osteoporosis Foundation's position statement on peak bone mass development and lifestyle factors: a systematic review and implementation recommendations. *Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA,* **27**(4): 1281-1386. doi: 10.1007/s00198-015-3440-3

Weaver, C. M., Gordon, C. M., Janz, K. F., Kalkwarf, H. J., Lappe, J. M., Lewis, R., O'Karma, M., Wallace, T. C. and Zemel, B. S. (2016). Erratum to: The National Osteoporosis Foundation's position statement on peak bone mass development and lifestyle factors: a systematic review and implementation recommendations. *Osteoporos Int,* **27**(4): 1387. doi: 10.1007/s00198-016-3551-5

Australia

Duque, G., Lord, S. R., Mak, J., Ganda, K., Close, J. J., Ebeling, P., Papaioannou, A. and Inderjeeth, C. A. (2016). Treatment of Osteoporosis in Australian Residential Aged Care Facilities: Update on Consensus Recommendations for Fracture Prevention. *J Am Med Dir Assoc,* **17**(9): 852-859. doi: 10.1016/j.jamda.2016.05.011

Ebeling, P. R., Seeman, E., Center, J., Chen, W., Chiang, C., Diamond, T., Duque, G., Eisman, J., Elliot, J., Ganda, K., Jesudason, D., Jones, G., Lyubomirsky, G., Major, G., Marabani, M., March, L., Prince, R., Seibel, M., Stuckey, B., Sztal-Mazer, S., Stanton, S., Waters, J. and White, C. (2021). *Position Statement on the Management of Osteoporosis*: HealthyBones Australia. **No RRs**

The Royal Australian College of General Practitioners and Osteoporosis Australia. (2017). *Osteoporosis prevention, diagnosis and management in postmenopausal women and men over 50 years of age.* . East Melbourne, Vic: RACGP. **No RRs of relevance**

Belgium

Sanchez-Rodriguez, D., Bergmann, P., Body, J. J., Cavalier, E., Gielen, E., Goemaere, S., Lapauw, B., Laurent, M. R., Rozenberg, S., Honvo, G., Beaudart, C. and Bruyère, O. (2020). The Belgian Bone Club 2020 guidelines for the management of osteoporosis in postmenopausal women. *Maturitas,* **139**: 69-89. doi: 10.1016/j.maturitas.2020.05.006

Verdonck, C., Annemans, L., Balligand, E., Goderis, G., Goemaere, S., Lapauw, B., Perkisas, S. and Borgermans, L. (2019). PMS52 CLINICAL GUIDELINE DEVELOPMENT FOR THE MANAGEMENT OF OSTEOPOROSIS IN POSTMENOPAUSAL WOMEN IN PRIMARY CARE. *Value in Health,* **22**: S703. doi: 10.1016/j.jval.2019.09.1596 [conference abstract] **No published guideline identified**

Verdonck, C., Goemare, S., Goderis, G. and ... (2020). *TREATMENT GUIDELINE FOR POSTMENOPAUSAL OSTEOPOROSIS MANAGEMENT IN PRIMARY CARE (Conference abstract)*. Paper presented at the OSTEOPOROSIS …. Retrieved from https://www.humacom.es/pdf/abstract/P1280.pdf [conference abstract] **No published guideline identified**

Canada

Toward Optimized Practice (TOP) Osteoporosis CPG Committee. (2016). *Diagnosis and management of osteoporosis clinical practice guideline.* Edmonton, AB: Toward Optimized Practice. **No RRs**

China

Chinese Society of Osteoporosis and Bone Mineral Research. (2017). Clinical guideline to prevention and treatment of osteoporosis. *… Journal of Osteoporosis,* **10**: 413-443. doi: 10.3969/j.issn.1674-2591.2017.05.002 **Not obtainable**

Ma, Y., Wang, Y. and Liu, Q. (2018). *China guideline for diagnosis andtreatment of senile osteoporosis*. **In Chinese translation required**

Ma, Y., Wang, Y., Liu, Q., Li, C., Ma, X., Wang, Y., Deng, L., He, L., Yang, N. and Chen, B. (2019). 2018 China guideline for diagnosis and treatment of senile osteoporosis. *Chinese Journal of Practical Internal Medicine,* **12**: 38-61. doi: I**n Chinese translation required**

Ma, Y., Wang, Y., Liu, Q., Li, C., Ma, X., Wang, Y., Deng, L., He, L., Yang, N., Chen, B., Qiu, G., Zhu, H., Tao, T., Qin, L., Wang, L. and Cheng, X. (2019). 2018 China guideline for the diagnosis and treatment of senile osteoporosis. *Chinese Journal of Gerontology,* **39**: 2561-2579. doi: – **In Chinese translation required**

Qiu, M. L., Xie, Y., Wang, X. H., Wang, X. Q., Zhao, D. B., Zhou, H. Q., Zhou, Y. Q., Yan, L., Liang, B. L., Shen, H. L., Cao, S. Y., Ding, Y., Gu, J. R., Zeng, X. F. and Yang, K. H. (2020). [Practice guideline for patients with osteoporosis]. *Zhonghua nei ke za zhi,* **59**(12): 953-959. doi: 10.3760/cma.j.cn112138-20200904-00792 – **In Chinese translation required**

Yijian, L., Yuan, H., Yue, Z., Shunwu, F., Buhuai, D., Changsheng, Z., Jingye, W., Yun, T., Zijun, G., Weimin, J., Qindong, S., Xiaohui, M., Jing, W., Yali, L., Honghui, Y., Yonghong, J., Shuixia, L., Lijun, H., Bo, L., Zhong, F., Baorong, H., Dingjun, H., Feng, L., Liang, Y., Yanzheng, G., Shiqing, F., Tiansheng, S., Dianming, J., Jiwei, T., Huan, W. and Yingze, Z. (2020). Consensus on standardized diagnosis and treatment for osteoporotic vertebral compression fracture patients during epidemic of corona virus disease 2019. *Chinese Journal of Trauma,* **36**(12). doi: 10.3760/CMA.J.ISSN.1001-8050.2020.02.004

Finland

A working group set up by the Duodecim of the Finnish Medical Association, the Finnish Association of Endocrinologists, the Finnish Gynecological Association and the Finnish Geriatrics Association. (2020). *Osteoporosis. Current care recommendation. [in Finnish]*. Helsinki: The Finnish Medical Society Duodecim.**No RRs of interest**

France

Bouvard, B., Briot, K., Legrand, E., Blain, H., Breuil, V., Chapurlat, R., Duquenne, M., Guggenbuhl, P., Lespessailles, E., Thomas, T. and Cortet, B. (2021). Recommandations françaises de la prise en charge et du traitement de l’ostéoporose masculine. *Revue du Rhumatisme,* **88**(3): 173-182. doi: <https://doi.org/10.1016/j.rhum.2021.02.024> **In French needs translating**

Briot, K., Roux, C., Thomas, T., Blain, H., Buchon, D., Chapurlat, R., Debiais, F., Feron, J. M., Gauvain, J. B., Guggenbuhl, P., Legrand, E., Lehr-Drylewicz, A. M., Lespessailles, E., Tremollieres, F., Weryha, G. and Cortet, B. (2018). 2018 update of French recommendations on the management of postmenopausal osteoporosis. *Joint Bone Spine,* **85**(5): 519-530. doi: 10.1016/j.jbspin.2018.02.009 **No RRs**

Germany

AWMF. (2017). *Prophylaxe, Diagnostik und Therapie der Osteoporose. S3-LL (DVO) [Long version, revised 2019]*: AWMF.

Blattert, T. R., Schnake, K. J., Gonschorek, O., Gercek, E., Hartmann, F., Katscher, S., Mörk, S., Morrison, R., Müller, M., Partenheimer, A., Piltz, S., Scherer, M. A., Ullrich, B. W., Verheyden, A. and Zimmermann, V. (2018). Nonsurgical and Surgical Management of Osteoporotic Vertebral Body Fractures: Recommendations of the Spine Section of the German Society for Orthopaedics and Trauma (DGOU). *Global Spine J,* **8**(2 Suppl): 50s-55s. doi: 10.1177/2192568217745823 **No relevant – focus is osteoporotic vertebral fracture treatment**

Blattert, T. R., Schnake, K. J., Gonschorek, O., Katscher, S., Ullrich, B. W., Gercek, E., Hartmann, F., Mörk, S., Morrison, R., Müller, M. L., Partenheimer, A., Piltz, S., Scherer, M. A., Verheyden, A. and Zimmermann, V. (2019). [Nonsurgical and surgical management of osteoporotic vertebral body fractures : Recommendations of the Spine Section of the German Society for Orthopaedics and Trauma (DGOU)]. *Orthopade,* **48**(1): 84-91. doi: 10.1007/s00132-018-03666-6 **Not guideline**

Neuerburg, C., Mittlmeier, L., Schmidmaier, R., Kammerlander, C., Bocker, W., Mutschler, W. and Stumpf, U. (2017). Investigation and management of osteoporosis in aged trauma patients: a treatment algorithm adapted to the German guidelines for osteoporosis. *J Orthop Surg Res,* **12**(1): 86. doi: 10.1186/s13018-017-0585-0 **Not guideline**

Niedhart, C. (2016). [Osteoporosis: Diagnostics and Therapy According to the German Guidelines]. *Z Orthop Unfall,* **154**(3): 237-244. doi: 10.1055/s-0041-110813 **No obtainable**

Pfeil, A., Lehmann, G. and Lange, U. (2018). [Update DVO guidelines 2017 on "Prophylaxis, diagnostics and treatment of osteoporosis in postmenopausal women and men" : What is new, what remains for rheumatologists?]. *Z Rheumatol,* **77**(9): 759-763. doi: 10.1007/s00393-018-0549-8 **Commentary/summary of AWMF guideline**

Thomasius, F., Baum, E., Bernecker, P. and ... (2018). DVO Leitlinie 2017 zur Prophylaxe, Diagnostik und Therapie der Osteoporose bei postmenopausalen Frauen und Männern: Kurtzversion. [S-3 DVO Guidelines 2017 in prophylaxis, diagnosis and therapy of osteoporosis in postmenopausal women und men: short version]. *Osteologie,* **27**(3): 154-160. doi: 10.1055/s-0038-1673537 **Commentary/summary of AWMF guideline**

Greece

Makras, P., Anastasilakis, A. D., Antypas, G., Chronopoulos, E., Kaskani, E. G., Matsouka, A., Patrikos, D. K., Stathopoulos, K. D., Tournis, S., Trovas, G. and Kosmidis, C. (2019). The 2018 Guidelines for the diagnosis and treatment of osteoporosis in Greece. *Arch Osteoporos,* **14**(1): 39. doi: 10.1007/s11657-019-0584-3 **No RR**

Italy

Nuti, R., Brandi, M. L., Checchia, G., Di Munno, O., Dominguez, L., Falaschi, P., Fiore, C. E., Iolascon, G., Maggi, S., Michieli, R., Migliaccio, S., Minisola, S., Rossini, M., Sessa, G., Tarantino, U., Toselli, A. and Isaia, G. C. (2019). Guidelines for the management of osteoporosis and fragility fractures. *Intern Emerg Med,* **14**(1): 85-102. doi: 10.1007/s11739-018-1874-2 **No RRs**

Rossini, M., Adami, S., Bertoldo, F., Diacinti, D., Gatti, D., Giannini, S., Giusti, A., Malavolta, N., Minisola, S., Osella, G., Pedrazzoni, M., Sinigaglia, L., Viapiana, O. and Isaia, G. C. (2016). Guidelines for the diagnosis, prevention and management of osteoporosis. *Reumatismo,* **68**(1): 1-39. doi: 10.4081/reumatismo.2016.870 **No RRs**

Sessa, G. (2017). Clinical guidelines for the prevention and treatment of osteoporosis from the Italian Society for Orthopaedics and Traumatology: preface. *J Orthop Traumatol,* **18**(Suppl 1): 1-2. doi: 10.1007/s10195-017-0475-6 **Not guideline – guideline preface only**

Tarantino, U., Iolascon, G., Cianferotti, L., Masi, L., Marcucci, G., Giusti, F., Marini, F., Parri, S., Feola, M., Rao, C., Piccirilli, E., Zanetti, E. B., Cittadini, N., Alvaro, R., Moretti, A., Calafiore, D., Toro, G., Gimigliano, F., Resmini, G. and Brandi, M. L. (2017). Clinical guidelines for the prevention and treatment of osteoporosis: summary statements and recommendations from the Italian Society for Orthopaedics and Traumatology. *J Orthop Traumatol,* **18**(Suppl 1): 3-36. doi: 10.1007/s10195-017-0474-7 **No RRs**

Poland

Lorenc, R., Gluszko, P., Franek, E., Jablonski, M., Jaworski, M., Kalinka-Warzocha, E., Karczmarewicz, E., Kostka, T., Ksiezopolska-Orlowska, K., Marcinowska-Suchowierska, E., Misiorowski, W. and Wiecek, A. (2017). Guidelines for the diagnosis and management of osteoporosis in Poland : Update 2017. *Endokrynol Pol,* **68**(5): 604-609. doi: 10.5603/EP.2017.0062 **No RRs**

Portugal

Marques, A., Rodrigues, A. M., Romeu, J. C., Ruano, A., Barbosa, A. P., Simões, E., Águas, F., Canhão, H., Alves, J. D., Lucas, R., Branco, J. C., Laíns, J., Mascarenhas, M., Simões, S., Tavares, V., Lourenço, O. and da Silva, J. A. (2016). Multidisciplinary Portuguese recommendations on DXA request and indication to treat in the prevention of fragility fractures. *Acta Reumatol Port,* **41**(4): 305-321. **No RRs**

Rodrigues, A. M., Canhão, H., Marques, A., Ambrósio, C., Borges, J., Coelho, P., Costa, L., Fernandes, S., Gonçalves, I., Gonçalves, M., Guerra, M., Marques, M. L., Pimenta, S., Pinto, P., Sequeira, G., Simões, E., Teixeira, L., Vaz, C., Vieira-Sousa, E., Vieira, R., Alvarenga, F., Araújo, F., Barcelos, A., Barcelos, F., Barros, R., Bernardes, M., Canas da Silva, J., Cordeiro, A., Costa, M., Cunha-Miranda, L., Cruz, M., Duarte, A. C., Duarte, C., Faustino, A., Figueiredo, G., Fonseca, J. E., Furtado, C., Gomes, J., Lopes, C., Mourão, A. F., Oliveira, M., Pimentel-Santos, F. M., Ribeiro, A., Sampaio da Nóvoa, T., Santiago, M., Silva, C., Silva-Dinis, A., Sousa, S., Tavares-Costa, J., Terroso, G., Vilar, A., Branco, J. C., Tavares, V., Romeu, J. C. and da Silva, J. (2018). Portuguese recommendations for the prevention, diagnosis and management of primary osteoporosis - 2018 update. *Acta reumatologica portuguesa,* **43**(1): 10-31.

Singapore

Agency for Care Effectiveness. (2018). *Osteoporosis — identification and management in primary care*. Singapore: ACE. **No RRs**

Spain

Caeiro-Rey, J. R., Ojeda-Thies, C., Cassinello-Ogea, C., Sáez-López, M. P., Etxebarría-Foronda, Í., Pareja-Sierra, T., Larrainzar-Garijo, R., Figueroa-Rodríguez, J., Freire Romero, A., Sende-Munin, N., Del Río-Pombo, E., Carro-Méndez, B., Mesa-Ramos, M., González-Macías, J. and Tarazona-Santabalbina, F. J. (2020). [COVID-19 and fragility hip fracture. Joint recommendations of the Spanish Society of Osteoporotic Fractures and the Spanish Society of Geriatrics and Gerontology]. *Rev Esp Geriatr Gerontol,* **55**(5): 300-308. doi: 10.1016/j.regg.2020.07.001 **No RR**

Naranjo Hernández, A., Díaz Del Campo Fontecha, P., Aguado Acín, M. P., Arboleya Rodríguez, L., Casado Burgos, E., Castañeda, S., Fiter Aresté, J., Gifre, L., Gómez Vaquero, C., Candelas Rodríguez, G., Francisco Hernández, F. M. and Guañabens Gay, N. (2019). Recommendations by the Spanish Society of Rheumatology on Osteoporosis. *Reumatol Clin (Engl Ed),* **15**(4): 188-210. doi: 10.1016/j.reuma.2018.09.004

Switzerland

Ferrari, S., Lippuner, K., Lamy, O. and Meier, C. (2020). 2020 recommendations for osteoporosis treatment according to fracture risk from the Swiss Association against Osteoporosis (SVGO). *Swiss Med Wkly,* **150**: w20352. doi: 10.4414/smw.2020.20352

Turkey

Kirazlı, Y., Atamaz Çalış, F., El, Ö., Gökçe Kutsal, Y., Peker, Ö., Sindel, D., Tuzun, Ş., Gogas Yavuz, D., Durmaz, B., Akarirmak, Ü., Bodur, H., Hamuryudan, V., Inceboz, U. and Öncel, S. (2020). Updated approach for the management of osteoporosis in Turkey: a consensus report. *Archives of Osteoporosis,* **15**(1): 137. doi: 10.1007/s11657-020-00799-0

Turkish Association of Endocrinology Metabolism. (2016). *Osteoporosis and Metabolic Bone Diseases Diagnosis and Treatment Guideline*: Miki Publishing Ltd İstanbul. Not obtainable

UK

British Menopause Society. (2018). *Prevention and treatment of osteoporosis in women*: BMS. M Not obtainable

Cooper, C., Javaid, K., Elliott, M., Stephens, D. and Tanna, N. (2020). *UK consensus guideline on the management of patients at low, high, and very high risk of osteoporotic fracture*: Guidelines. **No RRs**

Hampson, G., Stone, M., Lindsay, J. R., Crowley, R. K. and Ralston, S. H. (2021). Diagnosis and Management of Osteoporosis During COVID-19: Systematic Review and Practical Guidance. *Calcified tissue international*. doi: 10.1007/s00223-021-00858-9 **No RRs, is guideline relevant?**

National Institute for Health Care Excellence. (2017). *TA464: Bisphosphonates for treating osteoporosis [last updated July 2019]*: NICE. **No RRs**

National Institute for Health Care Excellence. (2017). *QS149: Osteoporosis*: NICE. **No RRs**

National Institute for Health Care Excellence. (2019). *CG146 Osteoporosis: assessing the risk of fragility fracture.*: NICE.

National Osteoporosis Guideline Group. (2019). *NOGG 2017: Clinical guideline for the prevention and treatment of osteoporosis*.

Compston, J., Cooper, A., Cooper, C., Gittoes, N., Gregson, C., Harvey, N., Hope, S., Kanis, J. A., McCloskey, E. V., Poole, K. E. S., Reid, D. M., Selby, P., Thompson, F., Thurston, A. and Vine, N. (2017). UK clinical guideline for the prevention and treatment of osteoporosis. *Arch Osteoporos,* **12**(1): 43. doi: 10.1007/s11657-017-0324-5 duplicate

National Osteoporosis Society. (2017). *Quality standards for osteoporosis and prevention of fragility fractures*: National Osteoporosis Society. **No RR**

SIGN. (2015). *SIGN 142: Management of osteoporosis and the prevention of fragility fractures [revised January 2021]*: SIGN.

# Table 1: Findings from search of Guideline research recommendations (RR) (2016-July 2021)

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Author | Country or Region | Organisation | Research recommendations (of relevance to bisphosphonates or treatment more broadly). | Research recommendation for stakeholder meeting (feeds into 2nd column of Table 2) |
| *Osteoporosis in General* | | |  |  |
| Allen *et al* (2017){#91} | USA | Institute for Clinical Systems Improvement | No official section on RR is present  Re: Anabolic Agents (Parathyroid hormone 1-34, Teriparatide)  “*Two comparative studies suggest that teriparatide may be superior to oral bisphosphonates in treating glucocorticoid-induced osteoporosis (Glüer, 2013; Saag, 2007). Further research is needed is this area.*” | Q29 What is the comparable safety, clinical and cost effectiveness of zoledronate? vs anabolic in people with steroid-induced osteoporosis? |
| Hauk *et al* (2018){#260} | USA | American College of Physicians | No official section on RR is present  Text offers the following:  “*Bisphosphonates should be offered to men with osteoporosis to decrease their risk of vertebral fracture. Most trials evaluating men with osteoporosis included women; therefore, specific research in men is needed.*” | Population in slides – to be considered for all |
| Eastell *et al* (2019){#80} | International | Endocrine Society | No official section on RR is present  Text offers the following:  “*Although there are some data suggesting that a lower dose of alendronate (5 mg/d) begun after 5 years of alendronate is equally effective in maintaining BMD and levels of BTMs, as is continuing the full dose (10 mg/d) (36), we do not know whether a dose reduction decreases AFF* [Atypical femoral fractures] *risk. Further study of this question might establish whether lowering the dose after 5 years might be an alternative to a bisphosphonate holiday.”* | Q14 Does dose reduction of bisphosphonate decrease the risk of atypical femur fractures for people with osteoporosis? |
| Kanis *et al* (2019){#35} | European | International Osteoporosis Foundation and European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis | No official section on RR is present  Text offers the following:  Re: adherence to treatment  “*Further research is required to optimise thresholds of compliance and persistence, the impact of gap length, offset times, and fraction of benefit*”  Re: Monitoring of treatment with biochemical markers of bone turnover”  “*More research is required using standardised analytes before robust evidence-based recommendations can be given*” | *Team discussion* -  Q10 What is the minimum level of average compliance with bisphosphonates needed for population clinical and cost effectiveness?  *Included in*  Q11 How can bisphosphonate effectiveness be defined, explained and monitored to promote medicines optimisation for people with osteoporosis? |
| Qaseem *et al* (2017){#90} | USA | American College of Physicians | ***“Future research:*** *Most of the evidence for treating osteoporotic men is based on trials that included women, and further research is needed on the treatment of men.*  *Studies directly addressing the efficacy of pharmacologic treatments for reducing fractures in patients with osteopenia are also needed.*”  ***“Inconclusive areas of evidence:*** *Comparative effectiveness trials evaluating pharmacologic treatments for low bone density or osteoporosis are lacking.*  *In addition, although FRAX scores are widely used, evidence linking FRAX scores to treatment efficacy is lacking.”* | Population in slides – to be considered for all  Q22 What is the comparable safety, clinical and cost effectiveness of zoledronate vs alendronate in people with osteoporosis or high fracture risk?  Q28 What is the comparable safety, clinical and cost effectiveness of zoledronate? vs anabolic in people with osteoporosis at very high fracture risk?  Q24 What is the comparable safety, clinical and cost effectiveness of zoledronate vs alendronate in men with osteoporosis? |
| Rodrigues *et al* (2018){#49} | Portugal | Portuguese Society of Rheumatology bone diseases’ working group organized meetings involving 55 participants (rheumatologists, rheumatology fellows and one OP specialist nurse) | “***Areas Where Evidence is Lacking:*** In the present OP recommendations, the SPR recommends FRAX® algorithm to evaluate individuals absolute risk of fracture. A recent randomized controlled trial revealed that FRAX® algorithm is a feasible and effective screening tool in reducing hip fractures157. However, it is important to note that evidence linking FRAX® scores to treatment efficacy is lacking158. In addition, comparative effectiveness trials evaluating pharmacologic treatments for low bone density or osteoporosis and high risk of fracture patients are also lacking119.” | Population in slides – to be considered for all  Q22 What is the comparable safety, clinical and cost effectiveness of zoledronate vs alendronate in people with osteoporosis or high fracture risk? |
| Naranjo Hernández *et al* (2019){#254} | Spain | Spanish Society of Rheumatology | No official section on RR is present  Text offers the following:  **Recommendation re:** use of bone turnover markers has not been established. However, they could be considered in initial assessment and in follow-up of patients with osteoporosis.  “*The majority of GPC recommend the consideration of the use ofMBT in the initial evaluation and in follow-up, as an additional test. In the initial evaluation, the high levels may predict a faster loss of*  *bone mass and a higher risk of fracture. But their main indication is in follow-up, since they can contribute to assessing treatment adherence and efficacy, and also contribute to monitoring the duration of therapeutic holidays. The groups of international experts conclude that further research studies are required prior to making a recommendation based on the evidence.*”  **Recommendation re:** Trabecular Bone Score  “*….the TBS could be an additional tool for the evaluation of fracture risk in patients with OP and in some causes of secondary OP (diabetes, hyperparathyroidism, glucocorticoids). However, its usefulness in the monitorisation of the therapeutic response has not yet been established.*  *To sum up, the panel of experts consider that although TBS could have several advantages in the evaluation of fracture risk, further studies are required to recommend its use in clinical practice.*” | Q11 How can bisphosphonate effectiveness be defined, explained and monitored to promote medicines optimisation for people with osteoporosis?  Q16 What is the role of bone turnover markers in determining the duration of treatment breaks? |
| Ferrari *et al* (2020) {#225} | Switzerland | Swiss Association against Osteoporosis (SVGO) | No official section on RR is present  Text offers the following:  **Recommendation re:**  osteoporosis treatment according to fracture risk (defining 4 risk categories)  “*Further studies are needed in Switzerland and elsewhere to evaluate whether such threshold captures a sufficient proportion of subjects effectively at very high risk, or on the contrary is too restrictive, which would call for adapting our guidelines in the future.*” | Team discussion - Out of scope |
| Kirazlı *et al* (2020) {#342} | Turkey | selected panel of Turkish experts in fields related to osteoporosis incl. representatives of several societies: The Turkish Osteoporosis Society, The Society of Endocrinology and Metabolism of Turkey, and The Turkish Society of Physical Medicine and Rehabilitation | No official section on RR is present  Text offers the following:  “*Academic institutions should encourage researchers to pursue further investigations on country-based clinical and epidemiological data to facilitate the prevention and treatment of osteoporosis*.” | No specific question |
| Compston *et al* (2017) {#183}  NOGG (2019)  {#75} | UK | NOGG | No official section on RR is present  Text offers the following:  “*Biochemical indices of skeletal turnover have the potential to aid risk assessment but probably play a more immediate role in the monitoring of treatment [42] (Evidence level Ia). Further research in this field is recommended so that their utility in clinical practice can be evaluated for use in diagnosis, prognosis and monitoring of treatment [43].”* | Q11 How can bisphosphonate effectiveness be defined, explained and monitored to promote medicines optimisation for people with osteoporosis? |
| NICE 2019 {#81} | UK | NICE | Provides recommendations re risk of fragility fracture, include the following  **Re:** FRAX and QFracture in adults receiving bone protective therapy - What is the utility of FRAX and QFracture in adults receiving bone protective therapy? | Team discussion -  Q18What is the role of FRAX in informing decisions about bisphosphonate treatment breaks? |
| SIGN 2021 {#82} | UK | SIGN | Research recommendations include:   * RCTs to evaluate the effects of osteoporosis therapies on clinical fractures in men * systematic reviews updated to incorporate all relevant evidence for the risk of MRONJ and atypical femoral fractures associated with bisphosphonate use * the optimal interval for repeat DXA measurement to monitor the effectiveness of osteoporosis treatments and the predictive value of these measurements in individual patients * randomised trials to determine if targeting treatment on the basis of high risk of fracture alone is an effective strategy for preventing fractures * trials to determine the efficacy of treatments, and duration of therapy for preventing rebound * randomised trials to evaluate the effects of osteoporosis treatments on non-vertebral fractures in patients with GIOP. | * Population in slides – to be considered for all * Q20 What is the incidence and what are the risk factors for bisphosphonates related osteonecrosis of the jaw and atypical femur fracture? * Q11 How can bisphosphonate effectiveness be defined, explained and monitored to promote medicines optimisation for people with osteoporosis? * Q22 * Out of scope (rebound fractures related to Denosumab) * Q23 What is the comparable safety, clinical and cost effectiveness of zoledronate vs alendronate in people with steroid induced osteoporosis? |
| *Post-menopausal women* | | |  |  |
| Sanchez-Rodriguez *et al* (2020) | Belgium | The Belgian Bone Club | No official section on RR is present  Text offers the following:  **Recommendations re:** If goals of pharmacological treatment of osteoporosis are not achieved  “*If the goals are not achieved, differential diagnosis with other diseases, adherence to treatment, reassessment of patients’ values and preferences, and risk level (low, high or very high) should be considered. However, the BBC board fully acknowledges that the evidence is limited for most of these recommendations and considers this topic a challenge for further research.*” | Team discussion -  Encompassed by monitoring  Q12 How do we define and manage treatment failure in people taking BP |
| *Older Adults* | | |  |  |
| Lems *et al* (2017)  {#79}  Adults > 50 years | European | European Federation of National Associations of Orthopaedics & Traumatology (EFORT) and European League Against Rheumatism (EULAR) | Research recommendations presented (Box 2), include the following:   * Role of muscle loss, sarcopenia and nutrition on recovery following hip fracture, and the role of physical and pharmacological approaches in managing these deficits * Optimal timing of start and duration of antiosteoporotic drugs * Benefits of combining exercise, nutrition, pharmacological and other intervention strategies * Effects of drugs (antiresorptive and osteoanabolic drugs, biologics, non-steroidal anti-inflammatory drugs) on fracture healing (delayed or non-union) and on atypical femoral fractures | * **Team discussion – out of scope** * **Q17 What is the optimal duration of treatment with bisphosphonates for people with osteoporosis?**   **q31 What is the comparable clinical and cost effectiveness of bisphosphonates combined with other approaches eg exercise, nutrition vs bisphosphonates alone in people with osteoporosis? Q21 What is the effect of bisphosphonates on fracture healing, in people with fragility and/or atypical femur fractures?** |
| *Frail Older Adults* | | |  |  |
| Rolland *et al* (2021){#329}  Recommendations for Research | International | International Conference on Frailty and Sarcopenia Research (ICFSR) Task Force 2020 | No official section on RR is present  Text offers the following:  Designing clinical trials to target bone fracture in frail older adults  “*To increase the efficiency and maximizing learnings from clinical studies, sponsors and researchers should use harmonized protocols with similar outcome measures. The ICFSR Task Force suggested*…” possible study designs, proposed outcomes, potential target population, design of interventions.  *“Clinical trials to test these interventions* [pharmacological and non-pharmacological]*, however, often exclude frail older persons because of comorbidities (such as mobility disability and cognitive impairment) or polypharmacy. The Task Force recommended that future clinical trials use harmonized protocols, including harmonized inclusion criteria and similar outcome measures; and that they test a range of multidomain therapies. They further advocated more high-quality research to develop interventions specifically for people who are frail and old.”* | Population in slides – to be considered for all, particularly  **Q26 What is the comparable safety, clinical and cost effectiveness of a single dose zoledronate in frail older person with very high fracture risk** |
| *Residential Aged Care Facilities* | | |  |  |
| Duque *et al* (2016) {#322} | Australia | Consensus Conference | No official section on RR is present  Text offers the following:  “*research in the field of fall and fracture prevention in RACFs, including major clinical trials, should be encouraged*” | Population in slides – to be considered for all, particularly Q26 as above |
| *Screening of adherence to oral bisphosphonates* | | |  |  |
| Diez-Perez *et al.* (2017){#274} | International | International Osteoporosis Foundation and the European Calcified Tissue Society Working group | **Recommendations re:** screening policy for assessing adherence to oral bisphosphonates given as treatment for osteoporosis, by measuring bone turnover markers PINP and CTX 3 months after starting therapy. (given findings of TRIO study which found the bone turnover markers, PINP and CTX can be used to identify low adherence in patients with postmenopausal osteoporosis initiating oral bisphosphonates for osteoporosis.)    No official section on RR is present  Text offers the following:  “*The results of the TRIO study refer to postmenopausal women in a given geographical area and, therefore, their translation to men and premenopausal patients as well as to other areas has to be extrapolated. …… more research on this aspect is needed and further validation of the results obtained in the TRIO study in different clinical trials and/or different drugs must be obtained to fully certify the proposed strategy.*” | **Q16 as above** |
| *Fragility fractures in context of Covid-19* | | |  |  |
| Caeiro-Rey *et al.* (2020) |  |  | No RR |  |

# Table 2: Uncertainties, source and record of discussion and output from Stakeholder Workshop 1

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| --- | --- | --- | --- | --- | --- |
| **GROUP 1** | | | | |  |
| **Theme** | **Uncertainty/Question** | **Source (where it arose from)**  P = interviews with people with osteoporosis; C = clinician interviews;  SRQ – Systematic review of qualitative research;  SRA – Systematic review on treatment adherence  SRMA – systematic review and network meta-analysis  HE – Health economic evaluation  CG – review of research recommendations from guidelines | **Notes to explain question further**  Text in italics pasted from clinical guideline review | **Questions for stakeholder meeting**  **If there is no question please consider your agreement with the question wording, including population, intervention, comparator and outcome as appropriate (for explanation of these terms please see slides)** | **Refined question following discussion in stakeholder meeting** |
| Patient factors influencing treatment selection and effectiveness | **1 How do we better *identify or predict* people with osteoporosis who will have difficulty (adhering to, or side effects with) bisphosphonates? AND/OR**  **2 What are the determinants (causes/risk factors) of non-adherence with oral bisphosphonates in people with osteoporosis?** | P  C  SRQ | Interviews demonstrated a number of people struggled to ‘get on’ with tablet bisphosphonates. The interview population may have been more well and more health literate than the general population.  Factors which appeared to influence people’s ability to ‘get on’ with tablet bisphosphonates   * Co-morbidities (particularly those which make sitting, standing or taking tablets difficult) * Taking multiple medicines, involving taking medication at different intervals * Age (identified as associated with forgetting) * Busy professional or social life vs stable routine * Lack of professional support * Live alone/lack home support (routines often involve partners/family members) * Beliefs – such as low concern/prioritisation of osteoporosis or anxious about medication * High health literacy [positively related] | Do we need both questions?  Do we need to know what factors are and how they interrelate before we can intervene? | **1 How do we better identifypeople with osteoporosis who will have difficulty taking or continuing with oral bisphosphonates?**  *Note from discussion – in first draft amendment to this question, persist used as lay term but has specific pharmacological definition, therefore alternative lay terms used – other option – ‘engage with’* |
| **3 How should patient characteristics and preferences influence selection of tablet vs injectable bisphosphonates to optimise medicine effectiveness in people with osteoporosis?** | P  C  SRQ | Patients are typically not offered choice. Availability of services and the referring clinician’s biases also affect the choices offered (or not offered)  Includes:  What is the role of patient choice?  What are the regional/service variations in ability to choose treatments?  Which patients should be considered for intravenous bisphosphonates first line? E.g. because they are likely to have difficulty taking the medicine (links to question above)  Also links to question 1/2 | Does question 3 include the additional Qs in the notes column or are other questions needed? | 2 Which people with osteoporosis should be offered intravenous bisphosphonates first line to optimise medicine effectiveness? |
| Patient support | **4 How can people with osteoporosis be supported to make decisions about, and adhere to oral bisphosphonates?** | P  C  SRQ | Patient participants reported finding it difficult to make decisions and unclear benefits of treatment  Links to question 5 | Can this be combined with question 5/6?  Do we need to reference specific populations in need – e.g. those with barriers to communication (e.g. visual, cognitive or hearing impairment) | 3. **How can people with osteoporosis be supported to make decisions about taking bisphosphonates?** |
| **5 What ongoing healthcare support do people with osteoporosis receiving tablet bisphosphonates need for medicines optimisation AND/OR**    **6 What is the long-term model of care for people taking tablet bisphosphonates?** | P  C  SRQ | Compared to people taking injectable bisphosphonates, patients receiving injectable bisphosphonates reported more care and support from health professionals and had their information needs met  Includes:  -What patterns/forms of follow up are appropriate after prescribing tablet bisphosphonate (e.g. three month telephone call)?  -What should follow up involve (outside of reporting bone densitometry testing), e.g. advice, signposting, options for other treatments?  -What difference does follow up make to patients’ ability to cope with and adhere to tablet bisphosphonates? | Is the question 5 ‘what’ or ‘how’?  What outcome should we include? Adherence vs medicines optimisation (medicine optimisation includes adherence, effectiveness and safety - see slides)  Does question 5/6 include the additional Qs in the notes column or are other questions needed?  Preference or 5 or 6 | 4. **What healthcare support do people with osteoporosis receiving bisphosphonates need for medicines optimisation?**  5 **What is the long-term model of care for people taking oral bisphosphonates in primary care?** |
| Clinician Support & policy | **7 What support do primary care practitioners need to identify appropriate treatment bisphosphonate regimens for people with osteoporosis?** | P  C  SRQ | Clinical decision making was very variable. GPs reported uncertainties about treatment  Includes:  How do primary care practitioners refer and make clinical decisions? | Is this just about identification?  No outcome in Q – does this matter?  Does question 7 include the additional Qs in the notes column or are other questions needed? | 6 **How can primary care practitioners be supported to make decisions about bisphosphonates with people with osteoporosis?** |
|  | **8 Which resources or incentives would encourage GP/primary care follow up of people with osteoporosis taking tablet bisphosphonates?** | P  C  SRQ | Osteoporosis is not currently a priority.  Includes:  what is the value of recall systems? | No outcome in Q – does this matter?  Also links to Q5.  Does Q8 include the additional Qs in the notes column or are other questions needed? | 7 **Which resources or incentives for primary care would optimise the use of bisphosphonates for people with osteoporosis?** |
|  | **9 How can a minimum standard of care be ensured for people with osteoporosis receiving bisphosphonates?** | P  C | Marked variability in care described by GPs. | No outcome  Do we need to define the standard of care first (see Q5) | 8 **How do we ensure quality standards are met for people with osteoporosis receiving bisphosphonates?** |
|  | **10 What is the minimum level of average compliance with bisphosphonates needed for population clinical and cost effectiveness?** | CG #35 | *Question from guidelines about modelling cost-effectiveness over populations* |  | 9. What proportion of a population need to adhere to their bisphosphonate to deliver clinical and cost effectiveness?  *Note from discussion – in first discussed amendment to this question ‘persist’ used for continuity with Q1 but now changed to more precise term* |
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| **GROUP 2** | | | | |  |
| **Theme** | **Uncertainty/Question** | **Source (where it arose from)**  P = interviews with people with osteoporosis; C = clinician interviews;  SRQ – Systematic review of qualitative research;  SRA – Systematic review on treatment adherence  SRMA – systematic review and network meta-analysis  HE – Health economic evaluation  CG – review of research recommendations from guidelines | **Notes to explain question further**  Text in italics pasted from clinical guideline review | **Questions for stakeholder meeting**  **If there is no question please consider your agreement with the question wording, including population, intervention, comparator and outcome as appropriate (for explanation of these terms please see slides)** | **Refined question following discussion in stakeholder meeting** |
| Monitoring and effectiveness | **11 How can bisphosphonate effectiveness be defined, explained and monitored to promote medicines optimisation for people with osteoporosis?** | P  C  SRQ  CG(#35 #254 #183 #274 #82) | Patients and clinicians described ambiguity about what treatment effectiveness is.  Clinical Guidelines list research recommendation: *-the optimal interval for repeat DXA measurement to monitor the effectiveness of osteoporosis treatments and the predictive value of these measurements in individual patients CG 82*  Includes:  -how can treatment effectiveness best be explained to patients to set realistic treatment expectations and promote treatment adherence?  -what is the value of monitoring with bone turnover markers and or bone densitometry  (including trabeculae bone score) ? | Does question 11 include the additional Qs in the notes column or are other questions needed? | 10 **How can oral bisphosphonate effectiveness be defined, explained and monitored to promote medicines optimisation for people with osteoporosis?** |
| **12 How do we define and manage treatment failure in people taking bisphosphonates?** | CG (Sanchez-Rodriguez *et al)* | *If the goals are not achieved, differential diagnosis with other diseases, adherence to treatment, reassessment of patients’ values and preferences, and risk level (low, high or very high) should be considered. However, the BBC board fully acknowledges that the evidence is limited for most of these recommendations and considers this topic a challenge for further research* |  | 11 **How do we define and manage treatment failure in people with osteoporosis taking bisphosphonates?** |
| **13 What are real-world discontinuation rates with zoledronate?** | SR | No UK data about how long people remain on treatment |  | 12 What different regimens of zoledronate are used in practice for people with osteoporosis and what is patients’ adherence to these regimens?  *Note from discussion: need to change discontinuation – and understand patterns of use as well (service level) as adherence* |
| Treatment breaks | **14 Does dose reduction of bisphosphonate decrease the risk of atypical femur fractures for people with osteoporosis? OR**  **15 Is lowering the dose of bisphosphonate an alternative approach to a drug holiday?** | CG *#80* | *Although there are some data suggesting that a lower dose of alendronate (5 mg/d) begun after 5 years of alendronate is equally effective in maintaining BMD and levels of BTMs, as is continuing the full dose (10 mg/d) (36), we do not know whether a dose reduction decreases AFF* [Atypical femoral fractures] *risk. Further study of this question might establish whether lowering the dose after 5 years might be an alternative to a bisphosphonate holiday* |  | 13 **Does dose reduction of bisphosphonate decrease the risk of atypical femur fractures for people with osteoporosis?**  **14 Is lowering the dose of bisphosphonate an alternative approach to a treatment break for people with osteoporosis?**  *Post meeting note: treatment break used instead of ‘drug holiday’ for consistency. Population added* |
| **16 What is the role of bone turnover markers in determining the duration of treatment breaks?** | CG *#254* | *But their main indication is in follow-up, since they can contribute to assessing treatment adherence and efficacy, and also contribute to monitoring the duration of therapeutic holidays. The groups of international experts conclude that further research studies are required prior to making a recommendation based on the evidence* |  | **15 What is the role of bone turnover markers in determining the duration of treatment breaks in people with osteoporosis?**  *Post meeting note: Population added* |
| **17 What is the optimal duration of treatment with bisphosphonates for people with osteoporosis?** | CG *#79* | *Optimal timing of start and duration of antiosteoporotic drugs* |  | **16 What is the optimal duration of treatment with bisphosphonates for people with osteoporosis?** |
| **18 What is the role of FRAX in informing decisions about bisphosphonate treatment breaks?** | CG #81 | *What is the utility of FRAX and QFracture in adults receiving bone protective therapy?* |  | 17 **What is the role of FRAX in informing decisions about bisphosphonate treatment breaks in people with osteoporosis?**  *Post meeting note: Population added* |
| Side effects/safety | **19 What is the comparable frequency and duration of adverse events (side effects) of the different bisphosphonates?** | SRMA | Limited data on duration and severity of adverse events e.g., flu like reaction. |  | **18 What is the comparable frequency and duration of adverse events (side effects) of the different bisphosphonates?** |
| **20 What is the incidence and what are the risk factors for bisphosphonates related osteonecrosis of the jaw and atypical femur fracture?** | CG *#82* | *systematic reviews updated to incorporate all relevant evidence for the risk of MRONJ and atypical femoral fractures associated with bisphosphonate use* |  | **19 What is the incidence and what are the risk factors for bisphosphonate (prescribed for osteoporosis) related osteonecrosis of the jaw and atypical femur fracture?** |
| Fracture healing | **21 What is the effect of bisphosphonates on fracture healing, in people with fragility and/or atypical femur fractures?** | CG *#79* | *Effects of drugs (antiresorptive and osteoanabolic drugs, biologics, non-steroidal anti-inflammatory drugs) on fracture healing (delayed or non-union) and on atypical femoral fractures* |  | **20 What is the effect of bisphosphonates on fracture healing, in people with fragility and atypical femur fractures?** |

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| **GROUP 3** | | | | |  |
| **Theme** | **Uncertainty/Question** | **Source (where it arose from)**  P = interviews with people with osteoporosis; C = clinician interviews.  SRQ – Systematic review of qualitative research.  SRA – Systematic review on treatment adherence  SRMA – systematic review and network meta-analysis  HE – Health economic evaluation  CG – review of research recommendations from guidelines | **Notes to explain question further**  Text in italics pasted from clinical guideline review | **Questions for stakeholder meeting**  **If there is no question please consider your agreement with the question wording, including population, intervention, comparator and outcome as appropriate (for explanation of these terms please see slides)** | **Refined question following discussion in stakeholder meeting** |
| Treatment comparisons | **22 What is the comparable safety, clinical and cost effectiveness of zoledronate vs alendronate in people with osteoporosis or high fracture risk?** | SRMA  CG #90 #49 #82 #329  HE | NICE recommend alendronate first line, our evidence suggests zoledronate more clinically effective and associated with better adherence than tablet bisphosphonates.  However, **outcomes** need to be fracture – hip and wrist fracture data in particular missing from current evidence, paucity of data regarding the occurrence of wrist and hip fractures. More data is needed regarding those two outcomes.  - Hip fractures: ALN, RIS, and ZOL were found to be statistically significant in decreasing the occurrence of hip fractures (only ZOL was clinical significant – but still the differences among the treatments were minimal).  - Wrist fractures: Although ZOL was found to be the most effective treatment, no statistical significant effect sizes were detected.  Need standardised measures **of adverse events and agreed terminology for adherence**  **Need more data on real world costs of administering zoledronate to determine cost-effectiveness and**  Population in current evidence – scarcity of men, people with steroid induced osteoporosis and cognitive impairment  Clinical Guidelines:  *randomised trials to determine if targeting treatment on the basis of high risk of fracture alone is an effective strategy for preventing fractures*  Populations prioritised in clinical guideline recommendations for further research  (particularly men,  people with osteopenia, populations defined by FRAX risk rather than BMD, frail older adults, steroid users - non-vertebral fractures | 25,26,27 best? | **21 What is the comparable safety, clinical and cost effectiveness of zoledronate vs alendronate in people at high risk of fracture?** |
| **23 What is the comparable safety, clinical and cost effectiveness of zoledronate vs alendronate in people with steroid induced osteoporosis?** | **22 What is the comparable safety, clinical and cost effectiveness of zoledronate vs alendronate in people with steroid induced osteoporosis?** |
| **24 What is the comparable safety, clinical and cost effectiveness of zoledronate vs alendronate in men with osteoporosis?** | **23 What is the best bisphosphonate choice and frequency for people who are unable to manage their medicines?**  *Post meeting note: add additional question to reflect discussion about people with cognitive impairment*  **24 What is the best bisphosphonate choice and frequency for people who are unable to manage their medicines specifically due to cognitive impairment?**  **25 What is the best bisphosphonate choice and frequency for people aged under 50 with osteoporosis?** |
| **25 What is the comparable safety, clinical and cost effectiveness of zoledronate vs alendronate in people with osteoporosis and cognitive impairment? Or**  **26 What is the comparable safety, clinical and cost effectiveness of a single dose zoledronate in frail older person with very high fracture risk OR**  **27 What is the best bisphosphonate regimen for people with cognitive impairment?** | *Notes from discussion – reflect different population groups in these questions. Discussion about licensed vs unlicensed*  *Post meeting note – changed regimen as was unclear in meeting* |
| **28 What is the comparable safety, clinical and cost effectiveness of zoledronate? vs anabolic in people with osteoporosis at very high fracture risk?** | SRMA  CG *.[#90] .[#91]*  CG #91 | NICE previously stated that bisphosphonates have equal effectiveness.  Our network meta-analysis shows that zoledronate is more clinically effective than oral bisphosphonates.  Guidelines recommend anabolic for those at very high fracture risk based on comparative trials showing anabolic are better than oral bisphosphonates.  *Clinical Guidelines state: Comparative effectiveness trials evaluating pharmacologic treatments for low bone density or osteoporosis are lacking*  *Two comparative studies suggest that teriparatide may be superior to oral bisphosphonates in treating glucocorticoid-induced osteoporosis Further research is needed is this area*  *Clinical Guidelines state:*  *Two comparative studies suggest that teriparatide may be superior to oral bisphosphonates in treating glucocorticoid-induced osteoporosis Further research is needed is this area* |  | **26 What is the comparable safety, clinical and cost effectiveness of zoledronate vs anabolic agents in people with osteoporosis at very high fracture risk?** |
| **29 What is the comparable safety, clinical and cost effectiveness of zoledronate? vs anabolic in people with steroid-induced osteoporosis?** |  | 27 **What is the comparable safety, clinical and cost effectiveness of zoledronate? vs anabolic agents in people with steroid-induced osteoporosis?** |
| **30 What is the comparable safety, clinical and cost effectiveness of ORAL ibandronate vs alendronate in people with osteoporosis?** | SRMA  HE | Less data on IBN effectiveness or adherence compared to other oral agents  Emerged from value of information analysis | What is the population? | 28 **What is the comparable safety, clinical and cost effectiveness of oral ibandronate vs alendronate in people with osteoporosis?** |
| **31 What is the comparable clinical and cost effectiveness of bisphosphonates combined with other approaches eg exercise, nutrition vs bisphosphonates alone in people with osteoporosis?** | CG*#79* | *Benefits of combining exercise, nutrition, pharmacological and other intervention strategies CG* |  | 29 **What is the comparable clinical and cost effectiveness of bisphosphonates combined with other non-pharmacological approaches vs bisphosphonates alone in people with osteoporosis?** |
| Treatment delivery issues | **32 What is the comparable safety, clinical and cost effectiveness of zoledronate administered in community (homes or GP surgeries) vs in hospital for people with osteoporosis?** | P  C | People with osteoporosis who received zoledronate at home valued the service and experience highly.  Estimates of costs of administering zoledronate have a large effect on whether it is cost-effective. No ‘real world’ data | Is this the right comparison or should it be alendronate?  What is the population? | 30 **What is the comparable safety, clinical and cost effectiveness of zoledronate administered in community (homes or GP surgeries) vs in hospital for people with osteoporosis?** |
| **33 What is the optimum frequency to give zoledronate to maximise clinical and cost effectiveness in people with osteoporosis?** | Study team | No data to our knowledge. Question from clinical practice. Zoledornate variably given annually or very 18 months, or longer |  | **31 What is the optimum frequency to give zoledronate to maximise clinical and cost effectiveness in people with osteoporosis?**  *Note from meeting – we talked about dividing this into subgroups again but now I have defined regimen above eg Q24 What is the best bisphosphonate choice and frequency for people aged under 50 with osteoporosis? I am not sure this is needed? – duplication?* |
| **34 What is the optimum dose of zoledronate in people with osteoporosis and renal impairment or low BMI to maximise safety and clinical effectiveness?** | Study team | No data to our knowledge. Question from clinical practice |  | **32 What is the best bisphosphonate choice, dose and frequency for people with low BMI or kidney impairment?**  *Post meeting note: add additional question to reflect recent publication about measuring renal function*  **33. What is the best way to measure renal function when considering bisphosphonate treatment?** |

Table 2: Verification of Research Questions as true uncertainties for prioritisation 11.01.22

Questions in italics arose from Systematic review, underlined questions are research recommendations (RR) identified from a search of recent (published in 2016 or later) international guidelines undertaken in July 2021 and do not need further verification that they are uncertainties

|  |  |  |
| --- | --- | --- |
| **Uncertainty** | **Evidence1** | **Notes** |
| Patient factors and patient support |  |  |
| 1. How do we better identify people with osteoporosis who will have difficulty taking or continuing with oral bisphosphonates? | No evidence identified |  |
| 1. Which people with osteoporosis should be offered **intravenous bisphosphonates first line** to optimise medicine effectiveness? | No evidence identified | Li N, Cornelissen D, Silverman S, Pinto D, Si L, Kremer I, Bours S, de Bot R, Boonen A, Evers S, van den Bergh J, Reginster JY, Hiligsmann M. An Updated Systematic Review of Cost-Effectiveness Analyses of Drugs for Osteoporosis. Pharmacoeconomics. 2021 Feb;39(2):181-209. doi: 10.1007/s40273-020-00965-9. Epub 2020 Oct 7. PMID: 33026634; PMCID: PMC7867562. - Includes IV bisphosphates, but doesn’t address which Pt should be offered these as first line to optimise effectiveness |
| 1. How can people with osteoporosis be **supported to make decisions** about taking bisphosphonates? | No evidence identified | NOGG –Recommendation - “*They* [commissioners of healthcare & DoH] *should ensure that accurate up-to-date information about the effects of pharmacological interventions is widely available to postmenopausal women and older men (>50 yrs) and their professional advisers so that patients may make an informed decision about their use.*” P.36 |
| 1. What **healthcare support** do people with osteoporosis receiving bisphosphonates need for medicines optimisation? | No evidence identified |  |
| 1. What is the **long-term model of care** for people taking oral bisphosphonates in **primary care?** | No evidence identified | [NOGG guideline] - SR re models of care for 2o prevention but 2013  Ganda K, Puech M, Chen JS et al. Models of care for the secondary prevention of osteoporotic fractures: a systematic review and meta-analysis. Osteoporos Int 2013;24:393-406.  Citation tracking of this paper identified a scoping review  Jones AR, Herath M, Ebeling PR, Teede H, Vincent AJ. Models of care for osteoporosis: A systematic scoping review of efficacy and implementation characteristics. Eclinicalmedicine. 2021 Aug;38:101022. DOI: 10.1016/j.eclinm.2021.101022 – may be of interest |
| Clinical support and policy |  |  |
| 1. How can **primary care practitioners** be supported to make decisions about bisphosphonates with people with osteoporosis? | No evidence identified |  |
| 1. Which resources or incentives for **primary care** would optimise the use of bisphosphonates for people with osteoporosis? | No evidence identified |  |
| 1. How do we **ensure quality standards** are met for people with osteoporosis receiving bisphosphonates? | No evidence identified |  |
| 1. What proportion of a population need to adhere to their bisphosphonate to deliver clinical and cost effectiveness? | -- | RR identified from recent guideline search |
| 1. How can oral bisphosphonate effectiveness be defined, explained and monitored to promote medicines optimisation for people with osteoporosis? | -- | RR identified from recent guideline search |
| 1. How do we define and manage treatment failure in people with osteoporosis taking bisphosphonates? | -- | RR identified from recent guideline search |
| 1. *What different regimens of zoledronate are used in practice for people with osteoporosis and what is patients’ adherence to these regimens?* | -- | None identified - Arose from Q from SR about absence of data on real world continuation rates (ZP) – SR reference? |
| Safety |  |  |
| 1. Does dose reduction of bisphosphonate decrease the risk of atypical femur fractures for people with osteoporosis? | -- | RR identified from recent guideline search |
| 1. Is lowering the dose of bisphosphonate an alternative approach to a treatment break for people with osteoporosis? | -- | RR identified from recent guideline search |
| 1. What is the role of bone turnover markers in determining the duration of treatment breaks in people with osteoporosis? | -- | RR identified from recent guideline search |
| 1. What is the optimal duration of treatment with bisphosphonates for people with osteoporosis? | -- | RR identified from recent guideline search |
| 1. What is the role of FRAX in informing decisions about bisphosphonate treatment breaks in people with osteoporosis? | -- | RR identified from recent guideline search |
| 1. *What is the comparable frequency and duration of adverse events (side effects) of the different bisphosphonates?* | -- | Not sure about this, emerged from SR but was not the question the SR asked, probably needs checking (ZP) – SR reference? |
| 1. What is the incidence and what are the risk factors for bisphosphonate (prescribed for osteoporosis) related osteonecrosis of the jaw and atypical femur fracture? | -- | RR identified from recent guideline search |
| 1. What is the effect of bisphosphonates on fracture healing, in people with fragility and atypical femur fractures? | -- | RR identified from recent guideline search |
| *Effectiveness* |  |  |
| 1. *What is the comparable safety, clinical and cost effectiveness of zoledronate vs alendronate in people at high risk of fracture?* | -- | None identified - Missing population from SR (ZP) – SR reference? |
| 1. What is the comparable safety, clinical and cost effectiveness of zoledronate vs alendronate in people with steroid induced osteoporosis? | -- | RR identified from recent guideline search |
| 1. What is the best bisphosphonate choice and frequency for people who are unable to manage their medicines? | -- | RR identified from recent guideline search |
| 1. What is the best bisphosphonate choice and frequency for people who are unable to manage their medicines specifically due to cognitive impairment? | -- | RR identified from recent guideline search |
| 1. What is the best bisphosphonate choice and frequency for people aged under 50 with osteoporosis? | -- | RR identified from recent guideline search |
| 1. What is the comparable safety, clinical and cost effectiveness of zoledronate vs anabolic agents in people with osteoporosis at very high fracture risk? | -- | RR identified from recent guideline search |
| 1. What is the comparable safety, clinical and cost effectiveness of zoledronate vs anabolic agents in people with steroid-induced osteoporosis? | -- | RR identified from recent guideline search |
| 1. *What is the comparable safety, clinical and cost effectiveness of oral ibandronate vs alendronate in people with osteoporosis?* | -- | This is the only one that we would have expected in the review. We didn’t include anabolic or steroid induced OP in review (ZP) – SR reference? |
| 1. What is the comparable clinical and cost effectiveness of bisphosphonates combined with other non-pharmacological approaches vs bisphosphonates alone in people with osteoporosis? | -- | RR identified from recent guideline search |
| Delivery |  |  |
| 1. What is the comparable safety, clinical and cost effectiveness of **zoledronate** administered in community (homes or GP surgeries) vs in hospital for people with osteoporosis? | No evidence identified | Li N, Cornelissen D, Silverman S, Pinto D, Si L, Kremer I, Bours S, de Bot R, Boonen A, Evers S, van den Bergh J, Reginster JY, Hiligsmann M. An Updated Systematic Review of Cost-Effectiveness Analyses of Drugs for Osteoporosis. Pharmacoeconomics. 2021 Feb;39(2):181-209. doi: 10.1007/s40273-020-00965-9. Epub 2020 Oct 7. PMID: 33026634; PMCID: PMC7867562. - Concerns all osteoporosis drugs, but no comparisons made between different settings |
| 1. What is the optimum frequency to give **zoledronate** to maximise clinical and cost effectiveness in people with osteoporosis? | No evidence identified | SIGN – Recommendation: “Zoledronic acid (5 mg, intravenously) annually for three years is recommended in postmenopausal women with osteoporosis. The clinical benefit of annual zoledronic acid in preventing fractures beyond three years is uncertain.” P.80 – based on RCTs of this specific dosing, no evidence identified for other dosing regimes.  Li N, Cornelissen D, Silverman S, Pinto D, Si L, Kremer I, Bours S, de Bot R, Boonen A, Evers S, van den Bergh J, Reginster JY, Hiligsmann M. An Updated Systematic Review of Cost-Effectiveness Analyses of Drugs for Osteoporosis. Pharmacoeconomics. 2021 Feb;39(2):181-209. doi: 10.1007/s40273-020-00965-9. Epub 2020 Oct 7. - Does not address optimum frequency of zoledronate |
| 1. What is the best bisphosphonate choice, dose and frequency for people with **low BMI** or **kidney** impairment? | **Kidney** impairment: no evidence identified  **Low BMI**: no evidence identified | **Kidney:** Hara, T., Hijikata, Y., Matsubara, Y. and Watanabe, N. (2021). Pharmacological interventions versus placebo, no treatment or usual care for osteoporosis in people with chronic kidney disease stages 3‐5D. Cochrane Database of Systematic Reviews(7). doi: 0.1002/14651858.CD013424.pub2 **-** addresses CKD (3-5) all drugs, no comparative analysis of different bisphosphonates |
| 1. What is the best way to measure **renal function** when considering bisphosphonate treatment? | No evidence identified |  |

1 For each uncertainty the following guidelines were searched (reference list checked for SRs and recent trials) in addition to SR search in Cochrane & PubMed

1. National Osteoporosis Guideline Group. (2019). *Clinical guideline for the prevention and treatment of osteoporosis*. National Osteoporosis Guideline Group.
2. National Institute for Health Care Excellence. (2019). *TA464: Bisphosphonates for treating osteoporosis*: NICE[published in 2017 with an update in July 2019 involving a review of evidence] -
3. Scottish Intercollegiate Guidelines Network (SIGN). Management of osteoporosis and the prevention of fragility fractures. Edinburgh: SIGN; 2021. (SIGN publication no. 142). [January 2021]. Available from URL: <http://www.sign.ac.uk>

Following SR may be of interest/contain some relevant information – but unable to access:

* Almohaileb FI, Rasheed Z. Comparing the efficacies of bisphosphonates' therapies for osteoporosis persistence and compliance: A Systematic Review. Curr Mol Med. 2021 Apr 13. doi: 10.2174/1566524021666210414100227. Epub ahead of print. PMID: 33855941.

# Pre-workshop activity: Final Blast Off Research Question list for prioritisation v1.0 24.1.22

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| --- |
| **Instructions**  We would like you to read and consider these and **rank what you think are the most important top twenty from 1-20,** with 1 being the most important and 20 being the least important. This will mean there will be 14 left which **are even less important** which are **not ranked** (because there are 34 in total).  If choosing 1-20 is difficult, please consider which are **most** important, **medium** importance and **least i**mportance.  There are no right or wrong answers. Please go with your gut feeling. If you want more guidance please see the workshop guide document. There is also a short glossary at the end of this document. |

|  |  |
| --- | --- |
|  | **Your ranking**  **1 (most important) to 20 (least important)**  **Leaving some blank (unranked)** |
| 1. **Patient factors and patient support** | |
| * 1. How do we better identify people with osteoporosis who will have difficulty taking or continuing with oral bisphosphonates? |  |
| * 1. Which people with osteoporosis should be offered intravenous bisphosphonates first line to optimise medicine effectiveness? |  |
| * 1. How can people with osteoporosis be supported to make decisions about taking bisphosphonates? |  |
| * 1. What healthcare support do people with osteoporosis receiving bisphosphonates need for medicines optimisation? |  |
| * 1. What is the long-term model of care for people taking oral bisphosphonates in primary care? |  |
|  |  |
| 1. **Clinical support and policy** | |
| * 1. How can primary care practitioners be supported to make decisions about bisphosphonates with people with osteoporosis? |  |
| * 1. Which resources or incentives for primary care would optimise the use of bisphosphonates for people with osteoporosis? |  |
| * 1. How do we ensure quality standards are met for people with osteoporosis receiving bisphosphonates? |  |
| * 1. What proportion of a population need to adhere to their bisphosphonate to deliver clinical and cost effectiveness? |  |
| * 1. How can oral bisphosphonate effectiveness be defined, explained and monitored to promote medicines optimisation for people with osteoporosis? |  |
| * 1. How do we define and manage treatment failure in people with osteoporosis taking bisphosphonates? |  |
| * 1. What different regimens of zoledronate are used in practice for people with osteoporosis and what is patients’ adherence to these regimens? |  |
|  |  |
| 1. **Safety** | |
| * 1. Does dose reduction of bisphosphonate decrease the risk of atypical femur fractures for people with osteoporosis? |  |
| * 1. Is lowering the dose of bisphosphonate an alternative approach to a treatment break for people with osteoporosis? |  |
| * 1. What is the role of bone turnover markers in determining the duration of treatment breaks in people with osteoporosis? |  |
| * 1. What is the optimal duration of treatment with bisphosphonates for people with osteoporosis? |  |
| * 1. What is the role of FRAX in informing decisions about bisphosphonate treatment breaks in people with osteoporosis? |  |
| * 1. What is the comparable frequency and duration of adverse events (side effects) of the different bisphosphonates? |  |
| * 1. What is the incidence and what are the risk factors for bisphosphonate (prescribed for osteoporosis) related osteonecrosis of the jaw and atypical femur fracture? |  |
| * 1. What is the effect of bisphosphonates on fracture healing, in people with fragility and atypical femur fractures? |  |
|  |  |
| 1. **Effectiveness** | |
| * 1. What is the comparable safety, clinical and cost effectiveness of zoledronate vs alendronate in people at high risk of fracture? |  |
| * 1. What is the comparable safety, clinical and cost effectiveness of zoledronate vs alendronate in people with steroid induced osteoporosis? |  |
| * 1. What is the best bisphosphonate choice and frequency for people who are unable to manage their medicines? |  |
| * 1. What is the best bisphosphonate choice and frequency for people who are unable to manage their medicines specifically due to cognitive impairment? |  |
| * 1. What is the best bisphosphonate choice and frequency for people aged under 50 with osteoporosis? |  |
| * 1. What is the comparable safety, clinical and cost effectiveness of zoledronate vs anabolic agents in people with osteoporosis at very high fracture risk? |  |
| * 1. What is the comparable safety, clinical and cost effectiveness of zoledronate vs anabolic agents in people with steroid-induced osteoporosis? |  |
| * 1. What is the comparable safety, clinical and cost effectiveness of oral ibandronate vs alendronate in people with osteoporosis? |  |
| * 1. What is the comparable clinical and cost effectiveness of bisphosphonates combined with other non-pharmacological approaches vs bisphosphonates alone in people with osteoporosis? |  |
|  |  |
| 1. **Delivery** | |
| * 1. What is the comparable safety, clinical and cost effectiveness of zoledronate administered in community (homes or GP surgeries) vs in hospital for people with osteoporosis? |  |
| * 1. What is the optimum frequency to give zoledronate to maximise clinical and cost effectiveness in people with osteoporosis? |  |
| * 1. What is the best bisphosphonate choice, dose and frequency for people with low BMI or kidney impairment? |  |
| * 1. What is the best way to measure renal (kidney) function when considering bisphosphonate treatment? |  |

**Glossary**

**Adhere/Adherence:** taking a medicine as recommended

**Anabolic agent:** alternative osteoporosis drug which builds bone strength

**Atypical femur fractures**: rare side effect associated with long term bisphosphonate use

**Bisphosphonate:** medicine for osteoporosis. Includes alendronate, ibandronate, zoledronate, risedronate

**BMI**: body mass index, measure of healthy weight

**Bone turnover markers:** blood test to measure bone activity/turnover

**FRAX:** online tool for estimating an individual’s chance of breaking a bone over 10 years

**Medicines optimisation:** improving safety and effectiveness of medicine, including supporting people to take it

**Regimen:** plan of taking drug, including choice of drug, dose and how often

# Figure 2: Research Questions ranked 11-20

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| --- |
| 1. **How can oral bisphosphonate effectiveness be defined, explained and monitored to promote medicines optimisation for people with osteoporosis?** 2. **How do we better identify people with osteoporosis who will have difficulty taking or continuing with oral bisphosphonates?** 3. **What is the optimum frequency to give zoledronate to maximise clinical and cost effectiveness in people with osteoporosis?** 4. **Is lowering the dose of bisphosphonate an alternative approach to a treatment break for people with osteoporosis?** 5. **What is the incidence and what are the risk factors for bisphosphonate (prescribed for osteoporosis) related osteonecrosis of the jaw and atypical femur fracture?** 6. **What is the best bisphosphonate choice and frequency for people who are unable to manage their medicines specifically due to cognitive impairment?** 7. **Which resources or incentives for primary care would optimise the use of bisphosphonates for people with osteoporosis?** 8. **How do we define and manage treatment failure in people with osteoporosis taking bisphosphonates?** 9. **What is the comparable safety, clinical and cost effectiveness of zoledronate vs alendronate in people at high risk of fracture?** 10. **What is the best bisphosphonate choice, dose and frequency for people with low BMI or kidney impairment?** |

# Figure 3: Unranked research questions

|  |
| --- |
| * What proportion of a population need to adhere to their bisphosphonate to deliver clinical and cost effectiveness? * What different regimens of zoledronate are used in practice for people with osteoporosis and what is patients’ adherence to these regimens? * Does dose reduction of bisphosphonate decrease the risk of atypical femur fractures for people with osteoporosis? * What is the role of FRAX in informing decisions about bisphosphonate treatment breaks in people with osteoporosis? * What is the comparable frequency and duration of adverse events (side effects) of the different bisphosphonates? * What is the effect of bisphosphonates on fracture healing, in people with fragility and atypical femur fractures? * What is the comparable safety, clinical and cost effectiveness of zoledronate vs alendronate in people with steroid induced osteoporosis? * What is the best bisphosphonate choice and frequency for people who are unable to manage their medicines? * What is the comparable safety, clinical and cost effectiveness of zoledronate vs anabolic agents in people with osteoporosis at very high fracture risk? * What is the comparable safety, clinical and cost effectiveness of zoledronate vs anabolic agents in people with steroid-induced osteoporosis? * What is the comparable  safety, clinical and cost effectiveness of oral ibandronate vs alendronate in people with osteoporosis? * What is the comparable clinical and cost effectiveness of bisphosphonates combined with other non-pharmacological approaches vs bisphosphonates alone in people with osteoporosis? * What is the best way to measure renal function when considering bisphosphonate treatment? |